

FORM PTO-1396 (Modified)
REV 11-2000

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

ATTORNEY'S DOCKET NUMBER

TRANSMITTAL LETTER TO THE UNITED STATES

DESIGNATED/ELECTED OFFICE (DO/EO/US)

CONCERNING A FILING UNDER 35 U.S.C. 371

215095US0PCT

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR

097926385

INTERNATIONAL APPLICATION NO.

PCT/JP00/02710

INTERNATIONAL FILING DATE

25 April 2000

PRIORITY DATE CLAIMED

27 April 1999

TITLE OF INVENTION

NEW COMPOUND

APPLICANT(S) FOR DO/EO/US

TOJO Takashi et al.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (24) indicated below.
4. ☒ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
 - a. ☐ is attached hereto (required only if not communicated by the International Bureau).
 - b. ☒ has been communicated by the International Bureau.
 - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
 - a. ☐ is attached hereto.
 - b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
 - a. ☐ are attached hereto (required only if not communicated by the International Bureau).
 - b. ☐ have been communicated by the International Bureau.
 - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
 - d. ☒ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
10. ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/ISPE/409).
12. ☒ A copy of the International Search Report (PCT/ISA/210).

Items 13 to 20 below concern document(s) or information included:

13. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☐ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
20. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
21. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
22. ☐ Certificate of Mailing by Express Mail
23. ☒ Other items or information:

Request for Consideration of Documents Cited in International Search Report**Request for Priority****PCT/IB/304****PCT/IB/308**

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR

091/926385

INTERNATIONAL APPLICATION NO.

PCT/JP00/02710

ATTORNEY'S DOCKET NUMBER

215095US0PCT

24. The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :

- ☐ Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO \$104.00
- ☒ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO \$890.00
- ☐ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO \$740.00
- ☐ International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) \$710.00
- ☐ International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) \$100.00

ENTER APPROPRIATE BASIC FEE AMOUNT =

\$890.00

Surcharge of \$130.00 for furnishing the oath or declaration later than months from the earliest claimed priority date (37 CFR 1.492 (e)).

☐ 20 ☐ 30

\$0.00

CLAIMS

NUMBER FILED

NUMBER EXTRA

RATE

Total claims 12 - 20 = 0 x \$18.00

\$0.00

Independent claims 1 - 3 = 0 x \$84.00

\$0.00

Multiple Dependent Claims (check if applicable) ☐

\$0.00

TOTAL OF ABOVE CALCULATIONS =

\$890.00

☐ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.

\$0.00

SUBTOTAL =

\$890.00

Processing fee of \$130.00 for furnishing the English translation later than months from the earliest claimed priority date (37 CFR 1.492 (f)).

☐ 20 ☐ 30 +

\$0.00

TOTAL NATIONAL FEE =

\$890.00

Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) (check if applicable).

☐

\$0.00

TOTAL FEES ENCLOSED =

\$890.00

Amount to be:
refunded \$
charged \$

- a. ☒ A check in the amount of \$890.00 to cover the above fees is enclosed.
- b. ☐ Please charge my Deposit Account No. _____ in the amount of _____ to cover the above fees. A duplicate copy of this sheet is enclosed.
- c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 15-0030. A duplicate copy of this sheet is enclosed.
- d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

Surinder Sachar
Registration No. 34,423

22850

SIGNATURE

Norman F. Oblon

NAME

24,618

REGISTRATION NUMBER

DATE

Oct. 24 2001

DESCRIPTION

CYCLIC HEXAPEPTIDES HAVING ANTIBIOTIC ACTIVITY

5 TECHNICAL FIELD

The present invention relates to new polypeptide compounds and salts thereof which are useful as a medicament.

BACKGROUND ART

- 10 In U.S. Pat. No. 5,376,634, 5,569,646, WO 96/11210 and WO 99/40108, there are disclosed the polypeptide compound and a pharmaceutically acceptable salt thereof, which have antimicrobial activities (especially antifungal activity).

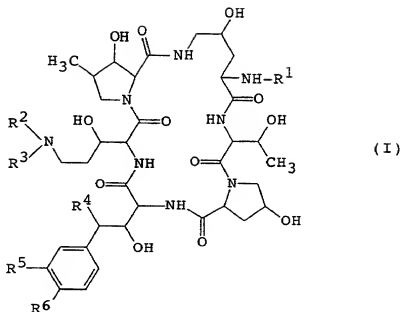
15 DISCLOSURE OF INVENTION

The present invention relates to new polypeptide compound and a salt thereof.

- More particularly, it relates to new polypeptide compound and a salt thereof, which have antimicrobial
- 20 activities [especially, antifungal activities, in which the fungi may include Aspergillus, Cryptococcus, Candida, Mucor, Actinomyces, Histoplasma, Dermatophyte, Malassezia, Fusarium and the like.], inhibitory activity on β -1,3-glucan synthase, and further which are expected to be useful for the
- 25 prophylactic and/or therapeutic treatment of Pneumocystis carinii infection (e.g. Pneumocystis carinii pneumonia) in a human being or an animal, to a process for preparation thereof, to a pharmaceutical composition comprising the same, and to a methods for the prophylactic and/or therapeutic
- 30 treatment of infectious disease including Pneumocystis carinii infection (e.g. Pneumocystis carinii pneumonia) in a human being or an animal.

- The object polypeptide compounds of the present
- 35 invention are new and can be represented by the following

general formula (I):



wherein

R¹ is hydrogen or acyl group,

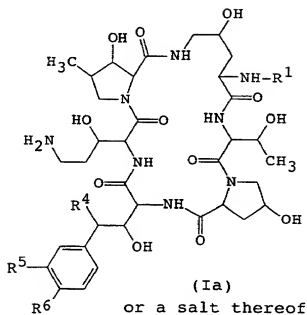
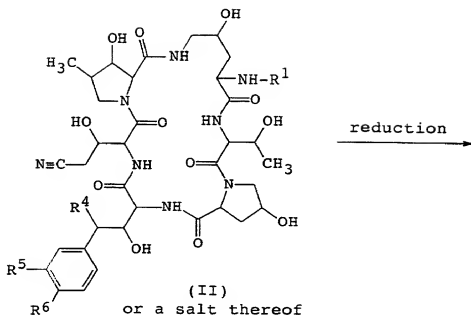
R² and R³ are independently hydrogen, lower alkyl which may have one or more suitable substituent(s), acyl group, heterocyclic group which may have one or more suitable substituent(s), lower alkylidenyl which may have one or more suitable substituent(s), higher alkyl which may have one or more suitable substituent(s) or cyano,

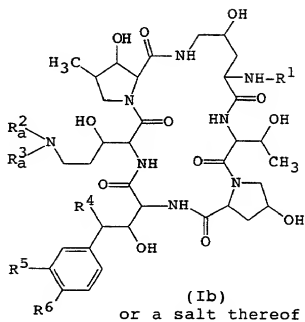
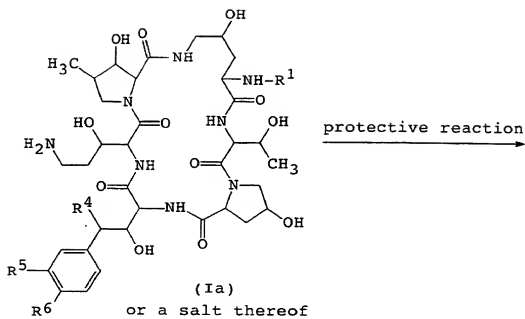
R⁴ is hydrogen or hydroxy,

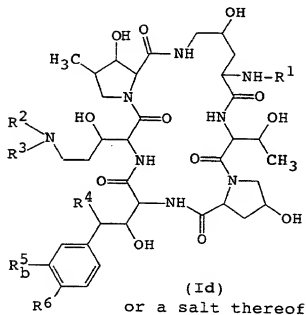
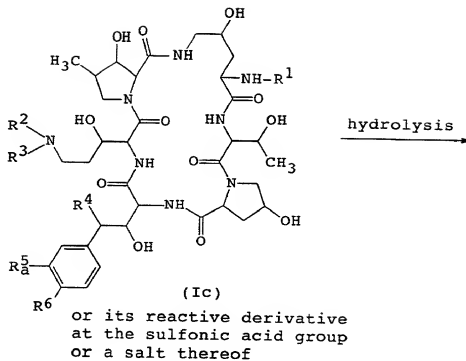
R⁵ is hydrogen, hydroxy, lower alkoxy or hydroxysulfonyloxy, and

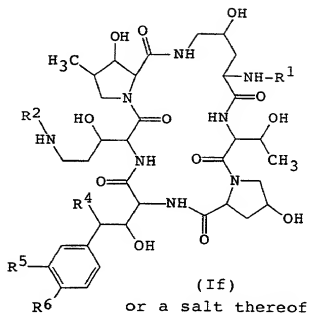
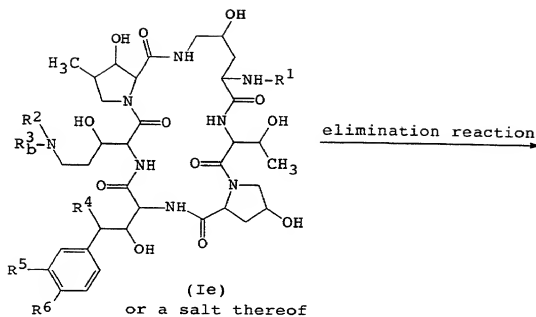
R⁶ is hydroxy or acyloxy, or a salt thereof.

The new polypeptide compound (I) or a salt thereof can be prepared by the process as illustrated in the following reaction schemes.

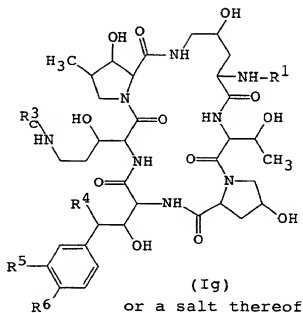
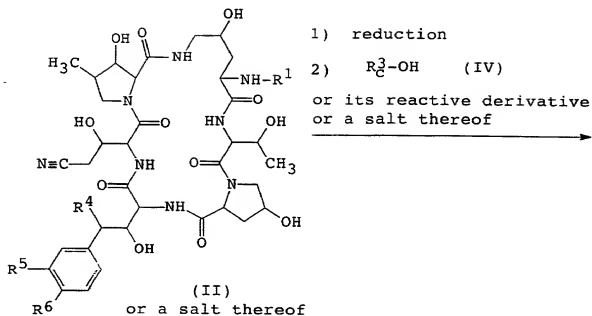
Process 1

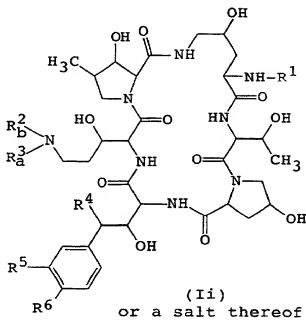
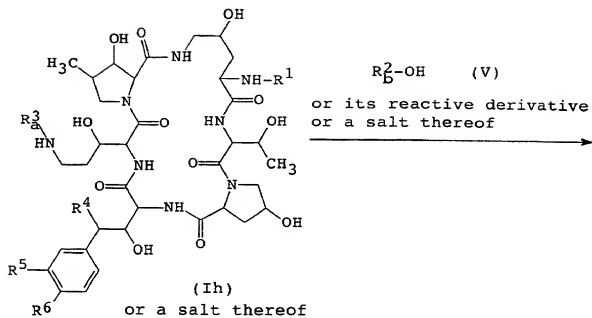
Process 2

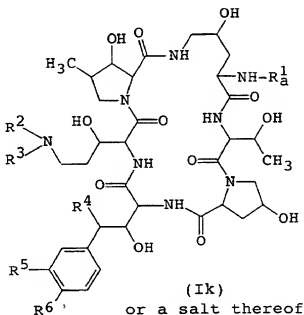
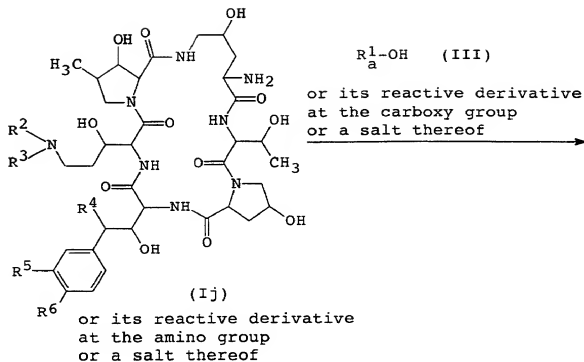
Process 3

Process 4

Process 5

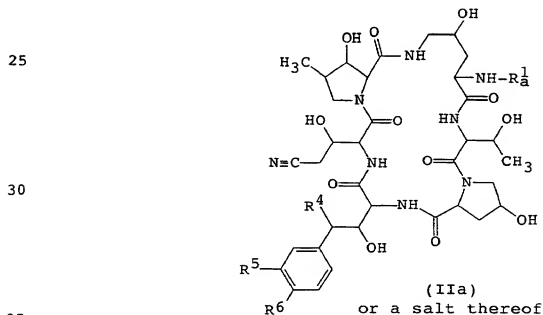
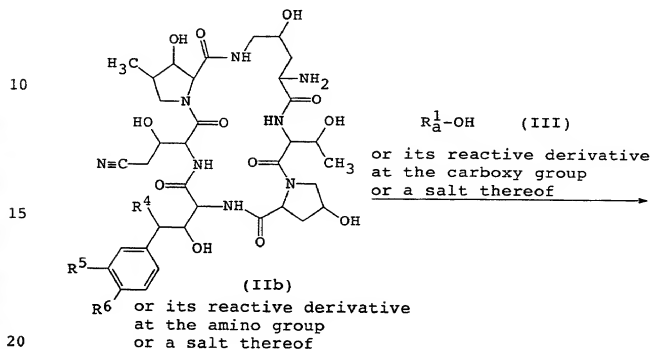


Process 6

Process 7

The Starting compound (II) or a salt thereof can be prepared by the process as illustrated in the following reaction scheme.

5 Process A



wherein R^1 , R^2 , R^3 , R^4 , R^5 and R^6 are defined above,

R_a^1 is acyl group,

R_a^2 is hydrogen, lower alkyl which may have one or more suitable substituent(s), acyl group, heterocyclic group which may have one or more suitable substituent(s), lower alkylidenyl which may have one or more suitable substituent(s), higher alkyl which may have one or more suitable substituent(s) or cyano,

R_B^2 is acyl group,

R_a^3 is lower alkyl which may have one or more suitable substituent(s), acyl group, heterocyclic group which may have one or more suitable substituent(s), lower alkylidenyl which may have one or more suitable substituent(s), higher alkyl which may have one or more suitable substituent(s) or cyano,

R_B^3 is amino protective group,

R_C^3 is acyl group,

R_a^5 is hydroxysulfonyloxy, and

R_B^5 is hydroxy.

Suitable salt of the new polypeptide compound (I) is a pharmaceutically acceptable and conventional non-toxic salt, and may include a salt with a base or an acid addition salt such as a salt with an inorganic base, for example, an alkali metal salt (e.g., sodium salt, potassium salt, etc.), an alkaline earth metal salt (e.g., calcium salt, magnesium salt, etc.), an ammonium salt; a salt with an organic base, for example, an organic amine salt (e.g., triethylamine salt, diisopropylethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt,

- N,N'-dibenzylethylenediamine salt, 4-dimethylaminopyridine salt, etc.);
- an inorganic acid addition salt (e.g., hydrochloride hydrobromide, sulfate, phosphate, etc.);
- 5 an organic carboxylic sulfonic acid addition salt (e.g., formate, acetate, trifluoroacetate, maleate, tartrate, fumarate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc.);
- a salt with a basic or acidic amino acid (e.g., arginine,
- 10 aspartic acid, glutamic acid, etc.).

Suitable examples and illustration of the various definitions in the above and subsequent descriptions of the present specification, which the present invention intends to include within the scope thereof, are explained in detail as follows:

The term "lower" is used to intend a group having 1 to 6 carbon atom(s), unless otherwise provided.

- Suitable example of "one or more" may be the number of 1
- 20 to 6, in which the preferred one may be the number of 1 to 3.

Suitable example of "halogen" may be fluorine, chlorine, bromine, iodine and the like.

- Suitable example of "lower alkoxy" may include straight or branched one such as methoxy, ethoxy, propoxy, isopropoxy,
- 25 butoxy, isobutoxy, tert-butoxy, pentyloxy, tert-pentyloxy, neo-pentyloxy, hexyloxy, isohexyloxy and the like.

- Suitable example of "higher alkoxy" may include straight or branched one such as heptyloxy, octyloxy,
- 3,5-dimethyloctyloxy, 3,7-dimethyloctyloxy, nonyloxy,
- 30 decyloxy, undecyloxy, dodecyloxy, tridecyloxy, tetradecyloxy, hexadecyloxy, heptadecyloxy, octadecyloxy, nonadecyloxy, icosyloxy, and the like.

- Suitable example of "lower alkyl" may include straight or branched one having 1 to 6 carbon atom(s), such as methyl,
- 35 ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-

butyl, pentyl, tert-pentyl, neo-pentyl, hexyl, isohexyl and the like.

Suitable example of "higher alkyl" may include straight or branched one such as heptyl, octyl, 3,5-dimethyloctyl, 3,7-dimethyloctyl, nonyl, decyl, undecyl, dodecyl, tridecyl, 5 tetradecyl, hexadecyl, heptadecyl, octadecyl, nonadecyl, icosyl, and the like.

Suitable example of "aryl" and "ar" moiety may include phenyl which may have lower alkyl (e.g., phenyl, mesityl, 10 xylyl, tolyl, etc.), naphthyl, anthryl, indanyl, fluorenyl, and the like, and this "aryl" and "ar" moiety may have one or more halogen.

Suitable example of "aroyl" may include benzoyl, toluoyl, naphthoyl, anthrylcarbonyl, and the like.

15 Suitable example of "heterocyclic group" may include unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, dihydropyridyl, pyrimidyl, pyrazinyl, 20 pyridazinyl, triazolyl (e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.), tetrazolyl (e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.), etc.;

saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 4 nitrogen 25 atom(s), for example, pyrrolidinyl, imidazolidinyl, piperidyl, piperazinyl, azetidiny, etc.;

unsaturated condensed heterocyclic group containing 1 to 4 nitrogen atom(s), for example, indolyl, isoindolyl, indolinyl, indoliziny, benzimidazolyl, quinolyl, 30 isoquinolyl, indazolyl, benzotriazolyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 35 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.), etc.;

saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, morpholinyl, sydnonyl, morpholino, etc.;

- 5 unsaturated condensed heterocyclic group containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, benzoxazolyl, benzoxadiazolyl, etc.;

- unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 or 2 sulfur
10 atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolyl, isothiazolyl, thiadiazolyl (e.g., 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.), dihydrothiazinyl, etc.;

- saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 or 2 sulfur
15 atom(s) and 1 to 3 nitrogen atom(s), for example thiazolidinyl, thiomorpholinyl, thiomorpholino, etc.;

- unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 or 2 sulfur
20 atom(s), for example, thienyl, dihydrodithiinyl, dihydrodithionyl, etc.;

 unsaturated condensed heterocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, benzothiazolyl, benzothiadiazolyl, imidazothiadiazolyl, etc.;

- 25 unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing an oxygen atom, for example, furyl etc.;

- saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 or 2 oxygen
30 atom(s), for example, tetrahydrofuran, tetrahydropyran, dioxacyclopentane, dioxacyclohexane, etc.;

- unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing an oxygen atom and 1 or 2 sulfur atom(s), for example, dihydrooxathiinyl,
35 etc.;

unsaturated condensed heterocyclic group containing 1 or 2 sulfur atom(s), for example benzothienyl, benzodithiynyl, etc.;

- 5 unsaturated condensed heterocyclic group containing an oxygen atom and 1 or 2 sulfur atom(s), for example, benzoxathiinyl, etc.; and the like, and this "heterocyclic group" may have one or more suitable substituent(s) selected from the group consisting of lower alkyl, oxo, cyclo(lower)alkyl, hydroxy(lower)alkyl,
- 10 carboxy(lower)alkanoyl which may have amino and heterocycliccarbonyl.

- Suitable example of "cyclo(lower)alkyl" may include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like, and this "cyclo(lower)alkyl" may have one or more lower alkyl.
- 15

Suitable example of "cyclo(lower)alkyloxy" may include cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, and the like.

- 20 Suitable example of "acyl group" may include aliphatic acyl, aromatic acyl, arylaliphatic acyl and heterocyclic-aliphatic acyl derived from carboxylic acid, carbonic acid, carbamic acid, sulfonic acid, and the like.

- 25 Suitable example of said "acyl group" may be illustrated as follows.

Carboxy; carbamoyl; mono or di(lower)alkylcarbamoyl (e.g., methylcarbamoyl, dimethylcarbamoyl, ethylcarbamoyl, diethylcarbamoyl, etc.)

30

- Aliphatic acyl such as lower or higher alkanoyl (e.g., formyl, acetyl, propanoyl, butanoyl, 2-methylpropanoyl, pentanoyl, 2,2-dimethylpropanoyl, hexanoyl, heptanoyl, octanoyl, nonanoyl, decanoyl, undecanoyl, dodecanoyl,
- 35 tridecanoyl, tetradecanoyl, pentadecanoyl, hexadecanoyl,

- heptadecanoyl, octadecanoyl, nonadecanoyl, icosanoyl, etc.);
lower or higher alkoxy carbonyl (e.g., methoxy carbonyl,
ethoxy carbonyl, t-butoxy carbonyl, t-pentyloxy carbonyl,
heptyloxy carbonyl, etc.); lower alkenyloxy carbonyl (e.g.,
5 vinyloxy carbonyl, propenyloxy carbonyl, allyloxy carbonyl,
butenyloxy carbonyl, butadienyloxy carbonyl,
pentyloxy carbonyl, hexenyloxy carbonyl, etc.);
lower or higher alkylsulfonyl (e.g., methylsulfonyl,
ethylsulfonyl, etc.);
- 10 lower or higher alkoxy sulfonyl (e.g., methoxy sulfonyl,
ethoxy sulfonyl, etc.); or the like;
- Aromatic acyl such as
aroyl (e.g., benzoyl, toluoyl, naphthoyl, etc.);
ar(lower)alkanoyl [e.g., phenyl(C₁-C₆)alkanoyl (e.g.,
15 phenylacetyl, phenylpropanoyl, phenylbutanoyl,
phenylisobutanoyl, phenylpentanoyl, phenylhexanoyl, etc.),
naphthyl(C₁-C₆)alkanoyl (e.g., naphthylacetyl,
naphthylpropanoyl, naphthylbutanoyl, etc.), etc.];
ar(lower)alkenoyl [e.g., phenyl(C₃-C₆)alkenoyl (e.g.,
20 phenylpropenoyl, phenylbutenoyl, phenylmethacryloyl,
phenylpentanoyl, phenylhexenoyl, etc.),
naphthyl(C₃-C₆)alkenoyl (e.g., naphthylpropenoyl,
naphthylbutenoyl, etc.), etc.];
ar(lower)alkoxy carbonyl [e.g., phenyl(C₁-C₆)alkoxy carbonyl
25 (e.g., benzyloxy carbonyl, etc.), fluorenyl(C₁-C₆)alkoxy-
carbonyl (e.g., fluorenylmethyloxy carbonyl, etc.), etc.];
aryloxy carbonyl (e.g., phenoxy carbonyl, naphthylloxy carbonyl,
etc.);
aryloxy(lower)alkanoyl (e.g., phenoxyacetyl,
30 phenoxypropionyl, etc.);
arylcarbamoyl (e.g., phenylcarbamoyl, etc.);
arylthiocarbamoyl (e.g., phenylthiocarbamoyl, etc.);
arylglyoxyloyl (e.g., phenylglyoxyloyl, naphthylglyoxyloyl,
etc.);
- 35 arylsulfonyl which may have 1 to 4 lower alkyl (e.g.,

phenylsulfonyl, p-tolylsulfonyl, etc.); or the like;

Heterocyclic acyl such as

heterocycliccarbonyl;

heterocyclic(lower)alkanoyl (e.g., heterocyclicacetyl,

5 heterocyclicpropanoyl, heterocyclicbutanoyl,

heterocyclicpentanoyl, heterocyclichexanoyl, etc.);

heterocyclic(lower)alkenoyl (e.g., heterocyclicpropenoyl,

heterocyclicbutenoyl, heterocyclicpentenoyl,

heterocyclichexenoyl, etc.);

10 heterocyclicglyoxyloyl; or the like;

in which suitable "heterocyclic" moiety in the terms

"heterocycliccarbonyl", "heterocyclic(lower)alkanoyl",

"heterocyclic(lower)alkenoyl" and "heterocyclicglyoxyloyl"

can be referred to aforementioned "heterocyclic" moiety, and

15 this "acyl group" may have one or more suitable

substituent(s) selected from the group consisting of lower

alkyl, oxo, amino and hydroxy.

Suitable example of "acyl group" of R^1 can be referred

20 to aforementioned "acyl group", in which the preferred one

may be aroyl which may have one or more suitable

substituent(s), lower alkoxy carbonyl, higher alkanoyl and

heterocycliccarbonyl which may have one or more suitable

substituent(s).

25

Suitable example of "suitable substituent(s)" in the

term of "aroyl substituted with one or more suitable

substituent(s)" and "heterocycliccarbonyl which may have one

or more suitable substituent(s)" may be heterocyclic group

30 substituted with aryl having lower alkoxy, heterocyclic group

substituted with aryl having lower alkoxy(lower)alkoxy,

heterocyclic group substituted with aryl having lower

alkoxy(higher)alkoxy, heterocyclic group substituted with

aryl having cyclo(lower)alkyloxy, heterocyclic group

35 substituted with aryl having heterocyclic group, heterocyclic

- group substituted with cyclo(lower)alkyl having cyclo(lower)alkyl, heterocyclic group substituted with aryl having aryl substituted with lower alkoxy(lower)alkoxy, heterocyclic group substituted with aryl having heterocyclic
- 5 group substituted with cyclo(lower)alkyl, heterocyclic group substituted with aryl having aryl substituted with heterocyclic group, heterocyclic group substituted with aryl having aryl substituted with lower alkoxy(lower)alkyl, heterocyclic group substituted with aryl having heterocyclic
- 10 group substituted with aryl(lower)alkoxy, heterocyclic group substituted with aryl having heterocyclic group substituted with lower alkoxy and aryl having halogen, heterocyclic group substituted with aryl having aryl substituted with lower alkoxy, heterocyclic group substituted with aryl having
- 15 cyclo(lower)alkyl, heterocyclic group substituted with aryl having heterocyclic group substituted with aryl, heterocyclic group substituted with aryl having heterocyclic group substituted with aryloxy, heterocyclic group substituted with aryl having heterocyclic group substituted with lower
- 20 alkoxy(lower)alkoxy, heterocyclic group substituted with aryl having heterocyclic group substituted with lower alkoxy(lower)alkylthio, heterocyclic group substituted with aryl having heterocyclic higher alkoxy, heterocyclic group substituted with aryl having heterocyclic group substituted
- 25 with cyclo(lower)alkyloxy, heterocyclic group substituted with aryl having heterocyclic group substituted with aryl having lower alkoxy(lower)alkoxy, heterocyclic group substituted with aryl having aryloxy(lower)alkoxy, heterocyclic group substituted with aryl having heterocyclic
- 30 group substituted with lower alkylthio, heterocyclic group substituted with aryl having heterocyclic group substituted with lower alkoxy and aryl, aryl substituted with heterocyclic group having aryl substituted with heterocyclic group, aryl substituted with lower alkoxy having
- 35 cyclo(lower)alkyl and amino, aryl substituted with

- heterocyclic group having cyclo(lower)alkyl, aryl substituted with lower alkoxy having cyclo(lower)alkyl and protected amino, aryl substituted with heterocyclic group having lower alkyl, aryl substituted with aryl having lower alkoxy,
- 5 heterocyclic group substituted with cyclo(lower)alkyl having lower alkyl, heterocyclic group substituted with cyclo(lower)alkyl having lower alkoxy and cyclo(lower)alkyl, heterocyclic group substituted with cyclo(lower)alkyl having cyclo(lower)alkyl substituted with lower alkoxy, heterocyclic
- 10 group substituted with aryl having lower alkoxy(lower)alkylsulfonyl, heterocyclic group substituted with aryl having lower alkoxy(higher)alkylsulfonyl, higher alkoxy, aryl substituted with lower alkoxy(higher)alkoxy, heterocyclic group substituted with aryl having higher
- 15 alkoxy, heterocyclic group substituted with higher alkyl, in which the preferred one may be unsaturated condensed heterocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having (C₄-C₆)-alkoxy, unsaturated 3 to 8-membered heteromonocyclic group
- 20 containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having (C₁-C₄)alkoxy(C₄-C₆)alkoxy, unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having (C₁-C₄)alkoxy(C₇-C₁₄)alkoxy, saturated 3
- 25 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with phenyl having (C₁-C₄)-alkoxy(C₇-C₁₄)alkoxy, unsaturated condensed heterocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having cyclo(C₄-C₆)alkyloxy,
- 30 unsaturated condensed heterocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having saturated 3 to 8-membered heteromonocyclic group containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), saturated 3 to 8-membered heteromonocyclic group
- 35 containing 1 to 4 nitrogen atom(s) substituted with cyclo-

- (C₄-C₆)alkyl having cyclo(C₄-C₆)alkyl, unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having phenyl substituted with (C₁-C₄)alkoxy(C₁-C₄)alkoxy,
- 5 unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with cyclo(C₄-C₆)alkyl, unsaturated condensed heterocyclic group
- 10 containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) having cyclo(C₄-C₆)alkyl,
- unsaturated 3 to 8-membered heteromonocyclic group
- 15 containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having (C₄-C₆)alkoxy,
- unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having cyclo(C₄-C₆)alkyl,
- 20 unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having phenyl substituted with (C₁-C₄)alkoxy,
- unsaturated 3 to 8-membered heteromonocyclic group
- 25 containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having phenyl substituted with (C₁-C₄)alkoxy(C₁-C₄)alkyl,
- unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s)
- 30 substituted with phenyl having phenyl substituted with saturated 3 to 8-membered heteromonocyclic group containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s) having di(C₁-C₄)alkyl.
- unsaturated 3 to 8-membered heteromonocyclic group
- 35 containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s)

- substituted with phenyl having saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with cyclo(C₄-C₆)alkyl having (C₁-C₄)alkyl, unsaturated 3 to 8-membered heteromonocyclic group
- 5 containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with phenyl.
- unsaturated 3 to 8-membered heteromonocyclic group
- 10 containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with phenoxy.
- unsaturated 3 to 8-membered heteromonocyclic group
- 15 containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with phenyl(C₁-C₄)alkoxy,
- unsaturated 3 to 8-membered heteromonocyclic group
- 20 containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with (C₁-C₄)alkoxy and chlorophenyl,
- unsaturated 3 to 8-membered heteromonocyclic group
- 25 containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having saturated 3 to 8-membered heteromonocyclic group containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s) substituted with di(C₁-C₄)alkyl,
- unsaturated 3 to 8-membered heteromonocyclic group
- 30 containing 1 to 4 nitrogen atom(s) substituted with phenyl having (C₇-C₁₄)alkoxy,
- unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having (C₄-C₆)alkoxy,
- 35 unsaturated 3 to 8-membered heteromonocyclic group

- containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having (C₁-C₄)alkoxy(C₄-C₆)alkoxy, unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s)
- 5 substituted with phenyl having (C₁-C₄)alkoxy(C₇-C₁₄)alkoxy, unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having (C₇-C₁₄)alkoxy substituted with saturated 3 to 8-membered heteromonocyclic group
- 10 containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s) having di(C₁-C₄)alkyl, unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having saturated 3 to 8-membered
- 15 heteromonocyclic group containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s) substituted with di(C₁-C₄)alkyl, unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 oxygen atom(s) and 1 to 4 nitrogen atom(s) substituted with phenyl having (C₁-C₄)alkoxy(C₇-C₁₄)-
- 20 alkylsulfonyl, saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with phenyl having (C₁-C₄)alkoxy(C₄-C₆)alkoxy, saturated 3 to 8-membered heteromonocyclic group
- 25 containing 1 to 4 nitrogen atom(s) substituted with phenyl having (C₁-C₄)alkoxy substituted with phenoxy, saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with phenyl having cyclo(C₄-C₆)alkyl,
- 30 saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with phenyl having phenyl substituted with (C₁-C₄)alkoxy(C₄-C₆)alkoxy, saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with phenyl
- 35 having phenyl substituted with saturated 3 to 8-membered

heteromonocyclic group containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s) substituted with di(C₁-C₄)alkyl,

saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with phenyl
5 having saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with cyclo-(C₄-C₆)alkyloxy,

saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with phenyl
10 having saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with phenyl,

saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with phenyl
having saturated 3 to 8-membered heteromonocyclic group
15 containing 1 to 4 nitrogen atom(s) substituted with phenyl having (C₁-C₄)alkoxy(C₄-C₆)alkoxy,

saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with phenyl
having saturated 3 to 8-membered heteromonocyclic group
20 containing 1 to 4 nitrogen atom(s) substituted with (C₁-C₄)alkylthio.

saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with phenyl
having saturated 3 to 8-membered heteromonocyclic group
25 containing 1 to 4 nitrogen atom(s) substituted with (C₁-C₄)alkoxy(C₄-C₆)alkylthio,

saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with phenyl
having saturated 3 to 8-membered heteromonocyclic group
30 containing 1 to 4 nitrogen atom(s) substituted with cyclo-(C₄-C₆)alkyl,

saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with phenyl
having saturated 3 to 8-membered heteromonocyclic group
35 containing 1 to 4 nitrogen atom(s) substituted with saturated

3 to 8-membered heteromonocyclic group containing 1 or 2 oxygen atom(s),

saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with phenyl
5 having saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with (C₁-C₄)alkoxy and phenyl,

saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with phenyl
10 having saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with (C₁-C₄)alkoxy and chlorophenyl,

saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with phenyl
15 having saturated 3 to 8-membered heteromonocyclic group containing 1 or 2 oxygen atom(s) and 1 to 4 nitrogen atom(s) substituted with di(C₁-C₄)alkyl,

saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with cyclo-
20 (C₄-C₆)alkyl having (C₄-C₆)alkyl,

saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with cyclo-(C₄-C₆)alkyl having cyclo(C₄-C₆)alkyl and (C₁-C₄)alkoxy,

saturated 3 to 8-membered heteromonocyclic group
25 containing 1 to 4 nitrogen atom(s) substituted with cyclo-(C₄-C₆)alkyl having cyclo(C₄-C₆)alkyl substituted with (C₁-C₄)alkoxy,

unsaturated condensed heterocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with
30 phenyl having (C₁-C₄)alkoxy(C₄-C₆)alkoxy,

unsaturated condensed heterocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having saturated 3 to 8-membered heteromonocyclic group 1 to 4 nitrogen atom(s) substituted with (C₁-C₄)alkoxy-
35 (C₁-C₆)alkoxy,

unsaturated condensed heterocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having saturated 3 to 8-membered heteromonocyclic group 1 to 4 nitrogen atom(s) substituted with (C₁-C₄)-alkoxy(C₄-C₆)alkylthio,

unsaturated condensed heterocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having saturated 3 to 8-membered heteromonocyclic group 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s) substituted with di(C₁-C₄)alkyl,

phenyl substituted with (C₁-C₄)alkoxy having cyclo-(C₄-C₆)alkyl and protected amino,

phenyl substituted with (C₁-C₄)alkoxy having cyclo-(C₄-C₆)alkyl and amino,

phenyl substituted with phenyl having (C₄-C₆)alkoxy, phenyl substituted with unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) having (C₄-C₆)alkyl,

phenyl substituted with saturated 3 to 8-membered

heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with cyclo(C₄-C₆)alkyl,

phenyl substituted with saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) having phenyl substituted with saturated 3 to 8-membered

heteromonocyclic group containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s) having di(C₁-C₄)alkyl,

phenyl substituted with condensed heterocyclic group containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s) having (C₄-C₆)alkyl,

(C₇-C₁₄)alkoxy,

unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with (C₇-C₁₄)alkyl,

unsaturated 3 to 8-membered heteromonocyclic group

containing 1 to 4 nitrogen atom(s) substituted with phenyl

having (C₄-C₆)alkoxy,

unsaturated 3 to 8-membered heteromonocyclic group
containing 1 to 4 nitrogen atom(s) substituted with phenyl
having saturated 3 to 8-membered heteromonocyclic group

5 containing 1 to 4 nitrogen atom(s),

xylyl substituted with (C₁-C₄)alkoxy(C₇-C₁₄)alkoxy,
and the most preferred one may be imidazothiadiazolyl
substituted with phenyl having pentyloxy, thiadiazolyl
substituted with phenyl having methoxyhexyloxy, thiadiazolyl
10 substituted with phenyl having methoxyoctyloxy, thiadiazolyl
substituted with phenyl having methoxyheptyloxy,

imidazothiadiazolyl substituted with phenyl having
cyclohexyloxy, imidazothiadiazolyl substituted with phenyl
having dimethylmorpholino, piperazinyl substituted with

15 phenyl having methoxyheptyloxy, piperazinyl substituted with
phenyl having methoxyoctyloxy, piperazinyl substituted with
cyclohexyl having cyclohexyl, thiadiazolyl substituted with
phenyl having phenyl substituted with methoxyethoxy,
thiadiazolyl substituted with phenyl having phenyl

20 substituted with methoxybutoxy, thiadiazolyl substituted with
phenyl having phenyl substituted with ethoxypropoxy,
imidazothiadiazolyl substituted with phenyl having
piperazinyl substituted with cyclohexyl, imidazothiadiazolyl
substituted with phenyl having piperazinyl substituted with
25 cyclohexyl,

thiazolyl substituted with phenyl having pentyloxy,
thiadiazolyl substituted with phenyl having
methoxyheptyloxy,

thiadiazolyl substituted with phenyl having cyclohexyl,
30 thiadiazolyl substituted with phenyl having
cyclohexyloxy,

thiadiazolyl substituted with phenyl having phenyl
substituted with propoxy,

thiadiazolyl substituted with phenyl having phenyl
35 substituted with ethoxymethyl,

thiadiazolyl substituted with phenyl having phenyl
substituted with methoxypropoxy,
thiadiazolyl substituted with phenyl having piperazinyl
substituted with cyclohexyl,
5 thiadiazolyl substituted with phenyl having phenyl
substituted with dimethylmorpholino,
thiadiazolyl substituted with phenyl having piperazinyl
substituted with methylcyclohexyl,
thiadiazolyl substituted with phenyl having piperidyl,
10 thiadiazolyl substituted with phenyl having piperidyl
substituted with phenyl,
thiadiazolyl substituted with phenyl having piperidyl
substituted with phenoxy,
thiadiazolyl substituted with phenyl having piperidyl
15 substituted with benzyloxy,
thiadiazolyl substituted with phenyl having piperidyl
substituted with methoxy and chlorophenyl,
thiadiazolyl substituted with phenyl having
dimethylmorpholino,
20 pyrimidinyl substituted with phenyl having octyloxy,
isoxazolyl substituted with phenyl having pentyloxy,
isoxazolyl substituted with phenyl having
methoxyhexyloxy,
isoxazolyl substituted with phenyl having
25 methoxyheptyloxy,
isoxazolyl substituted with phenyl having heptyloxy
substituted with dimethylmorpholino,
isoxazolyl substituted with phenyl having octyloxy
substituted with dimethylmorpholino,
30 isoxazolyl substituted with phenyl having
dimethylmorpholino,
oxadiazolyl substituted with phenyl having pentyloxy,
oxadiazolyl substituted with phenyl having
methoxyheptyloxy,
35 oxadiazolyl substituted with phenyl having

- methoxynonyloxy,
 oxadiazolyl substituted with phenyl having
methoxyheptylsulfonyl,
 oxadiazolyl substituted with phenyl having
5 methoxynonylsulfonyl,
 piperazinyl substituted with phenyl having
methoxyhexyloxy,
 piperazinyl substituted with phenyl having
methoxyheptyloxy,
10 piperazinyl substituted with phenyl having
phenoxypopoxy,
 piperazinyl substituted with phenyl having cyclohexyl,
 piperazinyl substituted with phenyl having phenyl
substituted with methoxypentyloxyphenyl,
15 piperazinyl substituted with phenyl having phenyl
substituted with dimethylmorpholino,
 piperazinyl substituted with phenyl having piperidyl
substituted with cyclohexyloxy,
 piperazinyl substituted with phenyl having piperidyl
20 substituted with phenyl,
 piperazinyl substituted with phenyl having piperidyl
substituted with methoxybutoxyphenyl,
 piperazinyl substituted with phenyl having piperidyl
substituted with propylthio,
25 piperazinyl substituted with phenyl having piperidyl
substituted with methoxyhexylthio,
 piperazinyl substituted with phenyl having piperidyl
substituted with cyclobutanespiro,
 piperazinyl substituted with phenyl having piperidyl
30 substituted with dioxacyclobutanespiro,
 piperazinyl substituted with phenyl having piperidyl
substituted with methoxy and phenyl,
 piperazinyl substituted with phenyl having piperidyl
substituted with methoxy and chlorophenyl,
35 piperazinyl substituted with phenyl having

- dimethylmorpholino,
piperazinyl substituted with cyclohexyl having tert-butyl,
piperazinyl substituted with cyclohexyl having
- 5 cyclohexyl and methoxy,
piperazinyl substituted with cyclohexyl having
cyclohexyl substituted with propoxy,
imidazothiadiazolyl substituted with phenyl having
methoxybutoxy,
- 10 imidazolthiadiazolyl substituted with phenyl having
cyclohexyloxy,
imidazothiadiazolyl substituted with phenyl having
piperazinyl substituted with cyclohexyl,
imidazolthiadiazolyl substituted with phenyl having
- 15 piperidyl substituted with methoxypropoxy,
imidazothiadiazolyl substituted with phenyl having
piperidyl substituted with methoxybutoxy,
imidazothiadiazolyl substituted with phenyl having
piperidyl substituted with methoxypentyloxy,
- 20 imidazothiadiazolyl substituted with phenyl having
piperidyl substituted with methoxyhexyloxy,
imidazothiadiazolyl substituted with phenyl having
piperidyl substituted with methoxyhexylthio,
imidazothiadiazolyl substituted with phenyl having
- 25 dimethylmorpholino,
phenyl substituted with propoxy having cyclohexyl and
tert-butoxycarbonylamino,
phenyl substituted with propoxy having cyclohexyl and
amino,
- 30 phenyl substituted with phenyl having pentyloxy,
phenyl substituted with thiazolyl having pentyl,
phenyl substituted with piperazinyl having cyclohexyl,
phenyl substituted with piperazinyl having phenyl
substituted with dimethylmorpholino,
- 35 phenyl substituted with bezoxazolyl having pentyl,

octyloxy,
pyrazolyl substituted with decyl,
pyrazolyl substituted with phenyl having hexyloxy,
pyrazolyl substituted with phenyl having piperidyl,
5 xyllyl substituted with methoxyheptyloxy.

- The more suitable example of "acyl group" may be benzoyl which has imidazolthiadiazolyl substituted with phenyl having pentyloxy, benzoyl which has thiadiazolyl substituted with phenyl having methoxyhexyloxy, benzoyl which has thiadiazolyl substituted with phenyl having methoxyoctyloxy, benzoyl which has thiadiazolyl substituted with phenyl having methoxyheptyloxy, benzoyl which has imidazothiadiazolyl substituted with phenyl having cyclohexyloxy, benzoyl which has imidazothiadiazolyl substituted with phenyl having
- 15 dimethylmorpholino, benzoyl which has piperazinyl substituted with phenyl having methoxyheptyloxy, benzoyl which has piperazinyl substituted with phenyl having methoxyoctyloxy, benzoyl which has piperazinyl substituted with cyclohexyl having cyclohexyl, benzoyl which has thiadiazolyl substituted
- 20 with phenyl having phenyl substituted with methoxyethoxy, benzoyl which has thiadiazolyl substituted with phenyl having phenyl substituted with methoxybutoxy, benzoyl which has thiadiazolyl substituted with phenyl having phenyl substituted with ethoxypropoxy, benzoyl which has
- 25 imidazothiadiazolyl substituted with phenyl having piperazinyl substituted with cyclohexyl, benzoyl which has imidazothiadiazolyl substituted with phenyl having piperazinyl substituted with cyclohexyl,
- benzoyl which has thiazolyl substituted with phenyl
- 30 having pentyloxy,
- benzoyl which has thiadiazolyl substituted with phenyl having methoxyheptyloxy,
- benzoyl which has thiadiazolyl substituted with phenyl having cyclohexyl,
- 35 benzoyl which has thiadiazolyl substituted with phenyl

having cyclohexyloxy,

benzoyl which has thiadiazolyl substituted with phenyl
having phenyl substituted with propoxy,

benzoyl which has thiadiazolyl substituted with phenyl
5 having phenyl substituted with ethoxymethyl,

benzoyl which has thiadiazolyl substituted with phenyl
having phenyl substituted with methoxypropoxy,

benzoyl which has thiadiazolyl substituted with phenyl
having phenyl substituted with dimethylmorpholino,

10 benzoyl which has thiadiazolyl substituted with phenyl
having piperazinyl substituted with cyclohexyl,

benzoyl which has thiadiazolyl substituted with phenyl
having piperazinyl substituted with methylcyclohexyl,

benzoyl which has thiadiazolyl substituted with phenyl
15 having piperidyl,

benzoyl which has thiadiazolyl substituted with phenyl
having piperidyl substituted with phenyl,

benzoyl which has thiadiazolyl substituted with phenyl
having piperidyl substituted with phenoxy,

20 benzoyl which has thiadiazolyl substituted with phenyl
having piperidyl substituted with benzyloxy,

benzoyl which has thiadiazolyl substituted with phenyl
having piperidyl substituted with methoxy and chlorophenyl,

benzoyl which has thiadiazolyl substituted with phenyl
25 having dimethylmorpholino,

benzoyl which has pyrimidinyl substituted with phenyl
having octyloxy,

benzoyl which has isoxazolyl substituted with phenyl
having pentyloxy,

30 benzoyl which has isoxazolyl substituted with pentyl
having methoxyhexyloxy,

benzoyl which has isoxazolyl substituted with phenyl
having methoxyheptyloxy,

benzoyl which has isoxazolyl substituted with phenyl
35 having heptyloxy substituted with dimethylmorpholino,

benzoyl which has isoxazolyl substituted with phenyl
having octyloxy substituted with dimethylmorpholino,

benzoyl which has isoxazolyl substituted with phenyl
having dimethylmorpholino,

5 benzoyl which has oxadiazolyl substituted with phenyl
having pentyloxy,

benzoyl which has oxadiazolyl substituted with phenyl
having methoxyheptyloxy,

10 benzoyl which has oxadiazolyl substituted with phenyl
having methoxynonyloxy,

benzoyl which has oxadiazolyl substituted with phenyl
having methoxyheptylsulfonyl,

benzoyl which has oxadiazolyl substituted with phenyl
having methoxynonylsulfonyl,

15 benzoyl which has piperazinyl substituted with phenyl
having methoxyhexyloxy,

benzoyl which has piperazinyl substituted with phenyl
having methoxyheptyloxy,

20 benzoyl which has piperazinyl substituted with phenyl
having phenoxypropoxy,

benzoyl which has piperazinyl substituted with phenyl
having cyclohexyl,

benzoyl which has piperazinyl substituted with phenyl
having phenyl substituted with methoxypentyloxyphenyl,

25 benzoyl which has piperazinyl substituted with phenyl
having phenyl substituted with dimethylmorpholino,

benzoyl which has piperazinyl substituted with phenyl
having piperidyl substituted with cyclohexyloxy,

30 benzoyl which has piperazinyl substituted with phenyl
having piperidyl substituted with phenyl,

benzoyl which has piperazinyl substituted with phenyl
having piperidyl substituted with methoxybutoxyphenyl,

benzoyl which has piperazinyl substituted with phenyl
having piperidyl substituted with propylthio,

35 benzoyl which has piperazinyl substituted with phenyl

- having piperidyl substituted with methoxyhexylthio,
benzoyl which has piperazinyl substituted with phenyl
having piperidyl substituted with cyclobutanespiro,
benzoyl which has piperazinyl substituted with phenyl
5 having piperidyl substituted with dioxacyclobutanespiro,
benzoyl which has piperazinyl substituted with phenyl
having piperidyl substituted with methoxy and phenyl,
benzoyl which has piperazinyl substituted with phenyl
having piperidyl substituted with methoxy and chlorophenyl,
10 benzoyl which has piperazinyl substituted with phenyl
having dimethylmorpholino,
benzoyl which has piperazinyl substituted with
cyclohexyl having tert-butyl,
benzoyl which has piperazinyl substituted with
15 cyclohexyl having cyclohexyl and methoxy,
benzoyl which has piperazinyl substituted with
cyclohexyl having cyclohexyl substituted with propoxy,
benzoyl which has imidazothiadiazolyl substituted with
phenyl having methoxybutoxy,
20 benzoyl which has imidazothiadiazolyl substituted with
phenyl having cyclohexyloxy,
benzoyl which has imidazothiadiazolyl substituted with
phenyl having piperazinyl substituted with cyclohexyl,
benzoyl which has imidazothiadiazolyl substituted with
25 phenyl having piperidyl substituted with methoxypropoxy,
benzoyl which has imidazothiadiazolyl substituted with
phenyl having piperidyl substituted with methoxybutoxy,
benzoyl which has imidazothiadiazolyl substituted with
phenyl having piperidyl substituted with methoxypropyloxy,
30 benzoyl which has imidazothiadiazolyl substituted with
phenyl having piperidyl substituted with methoxyhexyloxy,
benzoyl which has imidazothiadiazolyl substituted with
phenyl having piperidyl substituted with methoxyhexylthio,
benzoyl which has imidazothiadiazolyl substituted with
35 phenyl having dimethylmorpholino,

benzoyl which has phenyl substituted with propoxy having cyclohexyl and tert-butoxycarbonylamino,

benzoyl which has phenyl substituted with propoxy having cyclohexyl and amino,

5 benzoyl which has phenyl substituted with phenyl having pentyloxy,

benzoyl which has phenyl substituted with thiazolyl having pentyl,

10 benzoyl which has phenyl substituted with piperazinyl having cyclohexyl,

benzoyl which has phenyl substituted with piperazinyl having phenyl substituted with dimethylmorpholino,

benzoyl which has phenyl substituted with benzoxazolyl having pentyl,

15 benzoyl which has octyloxy,

thiadiazolylcarbonyl which has pyrazolyl substituted with decyl,

thiadiazolylcarbonyl which has pyrazolyl substituted with phenyl having hexyloxy,

20 thiadiazolylcarbonyl which has pyrazolyl substituted with phenyl having piperidyl,

piperazinylcarbonyl which has xylyl substituted with methoxyheptyloxy,

palmitoyl.

25

Suitable example of "lower alkyl" in the term of "lower alkyl which may have one or more suitable substituent(s)" can be referred to aforementioned "lower alkyl".

30 Suitable example of "suitable substituent(s)" in the term of "lower alkyl which may have one or more suitable substituent(s)" may be imino, amino, carbamoyl, lower alkoxy, heterocyclic group which may have one or more lower alkyl, carboxy, cyano(lower)alkylidene, lower alkylthio, sulfonic acid group, hydroxysulfonyloxy, and the like, in which the
35 preferred one may be imino, amino, carbamoyl, lower alkoxy,

pyrazolyl which may have lower alkyl, carboxy, hydroxy(lower)alkylamino which may have hydroxy(lower)alkyl, cyano(lower)alkylidene, lower alkylthio, sulfonic acid group or hydroxysulfonyloxy, and the more preferred one may be
5 imino, amino, carbamoyl, methoxy, pyrazolyl which may have methyl, carboxy, hydroxyethylamino which may have hydroxymethyl, cyanomethylidene, sulfonic acid group or hydroxysulfonyloxy.

Suitable example of "lower alkyl which may have one or
10 more suitable substituent(s)" may be iminomethyl, 1-iminoethyl, amidino, 1-imino-2-carbamoylethyl, 1-imino-3-methoxypropyl, carboxymethyl, 3-aminopropyl, 1-methylpyrazol-4-ylmethyl, methyl, pyrazolylmethyl having methyl, aminopropyl, aminobutyl, aminopentyl, carboxypentyl,
15 carboxymethyl, cyanomethylidenemethylthiomethyl, 2-cyano-1-methylthiovinyl, 2-cyano-1-aminovinyl, sulfopropyl, sulfobutyl, hydroxysulfonyloxypropyl and carboxyethyl.

Suitable example of "acyl group" of R^2 and R^3 can be
20 referred to aforementioned "acyl group", in which the preferred one may be lower alkanoyl, ar(lower)alkoxycarbonyl, lower alkenyloxycarbonyl, lower alkoxycarbonyl which may have lower alkanoyloxy, heterocyclic(lower)alkoxycarbonyl which may have oxo and lower alkyl, amino(lower)alkanoyl which may
25 have amino or hydroxy, heterocyclic(lower)alkanoyl which may have amino, sulfonic acid group, heterocycliccarbonyl, mono or di lower alkylcarbamoyl, and the most preferred one may be acetyl, sulfo, 2,5-diaminopentanoyl, fluorenylmethoxycarbonyl, allyloxycarbonyl, tert-
30 butoxycarbonyl, 1,3-dioxy-2-oxo-4-methyl-4-cyclopenten-5-ylmethoxycarbonyl, acetyloxymethoxycarbonyl, aminopropionyl, aminopentanoyl, aminohexanoyl, 5-amino-2-hydroxybutanoyl, 2,6-diaminohexanoyl, 2-amino-3-(pyrazol-4-yl)propionyl, morpholinocarbonyl, dimethylcarbamoyl, diethylcarbamoyl or
35 pyrrolidin-1-ylcarbonyl.

Suitable example of "suitable substituent(s)" in the term of "heterocyclic group which may have one or more suitable substituent(s)" of R^2 and R^3 may be lower alkyl, hydroxy(lower)alkyl, carboxy(lower)alkanoyl which may have amino and heterocycliccarbonyl, cyclo(lower)alkyl, oxo, and the like.

Suitable example of "heterocyclic group which may have one or more suitable substituent(s)" of R^2 and R^3 may be piperidyl which may have one or more suitable substituent(s) selected from the group consisting of lower alkyl, hydroxy(lower)alkyl, carboxy(lower)alkanoyl which may have amino and heterocycliccarbonyl; 1,3-dioxacyclohexyl which may have one or more suitable substituent(s) selected from the group consisting of lower alkyl and cyclo(lower)alkyl; thiopyranyl which may have one or more oxo; in which the most preferred one may be N,N-dimethylpiperidyl, N-hydroxyethyl-N-methylpiperidyl, carboxypropanoylpiperidyl, 4-amino-4-carboxybutanoylpiperidyl, azetidiny carbonylpiperidyl, dimethyl-1,3-dioxacyclohexyl, cyclohexyl-1,3-dioxacyclohexyl, dioxopyranyl.

Suitable example of "lower alkylidene which may have one or more suitable substituent(s)" of R^2 and R^3 may be lower alkylidene which may have one or more lower alkylamino, in which the preferred one may be dimethylaminomethylidene.

Suitable example of "higher alkyl which may have one or more suitable substituent(s)" of R^2 and R^3 may be higher alkyl which may have one or more carboxy, in which the preferred one may be carboxyoctyl.

Suitable example of "acyl" moiety of "acyloxy" can be referred to aforementioned "acyl group", in which the preferred one may be lower alkenyloxycarbonyl, and the most

preferred one may be allyloxycarbonyl.

Suitable example of "acyloxy" may be lower alkenyloxycarbonyloxy, and the more preferred one may be allyloxycarbonyloxy.

5

Suitable example of "amino protective group" may be included in aforementioned "acyl group", a conventional protective group such as ar(lower)alkoxycarbonyl and lower alkoxycarbonyl, in which the preferred one may be phenyl-
10 (C₁-C₄)alkoxycarbonyl and fluorenyl(C₁-C₄)alkoxycarbonyl and (C₁-C₄)alkoxycarbonyl, and the most preferred one may be benzyloxycarbonyl, fluorenylmethoxycarbonyl and tert-butoxycarbonyl.

15

Suitable example of "protected amino" may be amino substituted with aforementioned "acyl group", a conventional protected amino such as ar(lower)alkoxycarbonylamino and lower alkoxycarbonylamino, in which the preferred one may be phenyl(C₁-C₄)alkoxycarbonylamino and fluorenyl(C₁-C₄)-
20 alkoxycarbonylamino and (C₁-C₄)alkoxycarbonylamino, and the most preferred one may be benzyloxycarbonylamino, fluorenylmethoxycarbonylamino and tert-butoxycarbonylamino.

25

Particularly, the preferred examples of the compound (I) in the present invention are as follows:
the compound (I), wherein

R¹ is hydrogen; lower alkoxycarbonyl;

30

aroyl which has heterocyclic group substituted with aryl having a suitable substituent selected from the group consisting of lower alkoxy, lower alkoxy(lower)alkoxy, lower alkoxy(higher)alkoxy, aryl substituted with lower alkoxy(lower)alkoxy, cyclo(lower)alkyl, cyclo(lower)alkyloxy, aryl substituted with lower alkoxy, aryl substituted with lower alkoxy(lower)alkyl, aryl substituted

35

with heterocyclic group, heterocyclic group substituted with cyclo(lower)alkyl, heterocyclic group, heterocyclic group substituted with aryl, heterocyclic group substituted with aryloxy, 5 heterocyclic group substituted with ar(lower)alkoxy, heterocyclic group substituted with lower alkoxy and aryl, higher alkoxy, heterocyclic(higher)alkoxy, lower alkoxy(higher)alkylsulfonyl, aryloxy(lower)alkoxy, 10 heterocyclic group substituted with cyclo(lower)alkyloxy, heterocyclic group substituted with aryl having lower alkoxy(lower)alkoxy, heterocyclic group substituted with lower alkylthio, heterocyclic group 15 substituted with lower alkoxy(lower)alkylthio, and heterocyclic group substituted with lower alkoxy(lower)alkoxy;

aryloxy which has aryl substituted with a suitable substituent selected from the group consisting of lower alkoxy having cyclo(lower)alkyl and amino, lower alkoxy having cyclo(lower)alkyl and protected amino, aryl having lower alkoxy, heterocyclic group having lower alkyl, heterocyclic group having cyclo(lower)alkyl, and heterocyclic group having aryl substituted with heterocyclic group; 20

aryloxy which has heterocyclic group substituted with cyclo(lower)alkyl having one or more suitable substituent(s) selected from the group consisting of lower alkyl, lower alkoxy, cyclo(lower)alkyl, and cyclo(lower)alkyl substituted with lower alkoxy; 30

higher alkanoyl;

aryloxy which has higher alkoxy; or

35 heterocycliccarbonyl which has a suitable

substituent(s) selected from the group consisting of heterocyclic group substituted with higher alkyl, heterocyclic group substituted with aryl having lower alkoxy, heterocyclic group substituted with aryl having heterocyclic group, and aryl substituted with lower alkoxy(higher)alkoxy, 5
 R^2 and R^3 are independently hydrogen;

lower alkyl which may have one or more suitable substituent(s) selected from the group consisting of amino, carboxy, sulfinic acid group, 10
sulfonic acid group, hydroxy(lower)alkylamino which may have hydroxy(lower)alkyl, hydroxysulfonyloxy, imino, lower alkoxy, oxo, lower alkylthio, cyano(lower)alkylidene, and heterocyclic group which may have one or more lower alkyl; 15

lower alkoxycarbonyl which may have one or more suitable substituent(s) selected from the group consisting of lower alkanoyloxy and heterocyclic group; 20

lower alkenyloxycarbonyl;

ar(lower)alkoxycarbonyl;

lower alkanoyl which may have one or more suitable substituent(s) selected from the group consisting of amino, hydroxy and heterocyclic group; 25

heterocycliccarbonyl;

mono or di(lower)alkylcarbamoyl;

sulfonic acid group;

heterocyclic group which may have one or more suitable substituent(s) selected from the group consisting of lower alkyl, hydroxy(lower)alkyl, carboxy(lower)alkanoyl which may have amino, heterocycliccarbonyl, cyclo(lower)alkyl, and oxo; 30

lower alkylidene which may have mono or di lower alkylamino; 35

carboxy(higher)alkyl or
cyano;

R⁴ is hydrogen or hydroxy;

R⁵ is hydrogen, hydroxy, lower alkoxy or

5 hydroxysulfonyloxy; and

R⁶ is hydroxy or lower alkenyloxycarbonyloxy,

the more preferred one is the compound (I), wherein

R¹ is hydrogen; (C₁-C₄)alkoxycarbonyl;

10 benzoyl which has thiazolyl substituted with
phenyl having (C₄-C₆)alkoxy;

benzoyl which has thiadiazolyl substituted
with phenyl having a suitable substituent selected
from the group consisting of (C₁-C₄)alkoxy(C₄-C₆)-
alkoxy, phenyl substituted with (C₁-C₄)alkoxy-
15 (C₁-C₄)alkoxy, (C₁-C₄)alkoxy(C₇-C₁₄)alkoxy, cyclo-
(C₄-C₆)alkyl, cyclo(C₄-C₆)alkyloxy, phenyl
substituted with (C₁-C₄)alkoxy, phenyl substituted
with (C₁-C₄)alkoxy(C₁-C₄)alkyl, phenyl substituted
with di(C₁-C₄)alkylmorpholino, piperazinyl
20 substituted with cyclo(C₄-C₆)alkyl, piperazinyl
substituted with cyclo(C₄-C₆)alkyl having
(C₁-C₄)alkyl; piperidyl, piperidyl substituted with
phenyl, piperidyl substituted with phenoxy,
piperidyl substituted with benzyloxy, piperidyl
25 substituted with (C₁-C₄)alkoxy and chlorophenyl,
and phenyl having di(C₁-C₄)alkylmorpholino;

benzoyl which has pyrimidinyl substituted with
phenyl having (C₇-C₁₄)alkoxy;

30 benzoyl which has isoxazolyl substituted with
phenyl having a suitable substituent selected from
the group consisting of (C₄-C₆)alkoxy,
(C₁-C₄)alkoxy(C₄-C₆)alkoxy, (C₁-C₄)alkoxy(C₇-C₁₄)-
alkoxy, (C₇-C₁₄)alkoxy substituted with di(C₁-C₄)-
alkylmorpholino, and di(C₁-C₄)alkylmorpholino;

35 benzoyl which has oxadiazolyl substituted with

phenyl having a suitable substituent selected from the group consisting of (C₄-C₆)alkoxy, (C₁-C₄)-alkoxy(C₇-C₁₄)alkoxy, (C₁-C₄)alkoxy(C₇-C₁₄)alkoxy, and (C₁-C₄)alkoxy(C₇-C₁₄)alkylsulfonyl;

5 benzoyl which has piperazinyl substituted with phenyl having a suitable substituent selected from the group consisting of (C₁-C₄)alkoxy(C₄-C₆)alkoxy, (C₁-C₄)alkoxy(C₇-C₁₄)alkoxy, phenoxy(C₁-C₄)alkoxy, cyclo(C₄-C₆)alkyl, phenyl substituted with (C₁-C₄)-alkoxy(C₄-C₆)alkoxyphenyl, phenyl substituted with
10 di(C₁-C₄)alkylmorpholino, piperidyl substituted with cyclo(C₄-C₆)alkyloxy, piperidyl substituted with phenyl, piperidyl substituted with (C₁-C₄)-alkoxy(C₁-C₄)alkoxyphenyl, piperidyl substituted with (C₁-C₄)alkylthio, piperidyl substituted with
15 (C₁-C₄)alkoxy(C₄-C₆)alkylthio, piperidyl substituted with cyclo(C₄-C₆)alkanespiro, piperidyl substituted with dioxacyclo(C₄-C₆)alkanespiro, piperidyl substituted with (C₁-C₄)alkoxy and phenyl, piperidyl substituted with (C₁-C₄)alkoxy
20 and chlorophenyl, and di(C₁-C₄)alkylmorpholino;

benzoyl which has piperazinyl substituted with cyclo(C₄-C₆)alkyl having a suitable substituent selected from the group consisting of cyclo(C₄-C₆)-alkyl, (C₄-C₆)alkyl, cyclo(C₄-C₆)alkyl and (C₁-C₄)-alkoxy, and cyclo(C₄-C₆)alkyl substituted with
25 (C₁-C₄)alkoxy;

benzoyl which has imidazolthiadiazolyl substituted with phenyl having a suitable
30 substituent selected from the group consisting of (C₄-C₆)alkoxy, (C₁-C₄)alkoxy(C₄-C₆)alkoxy, cyclo-(C₄-C₆)alkyloxy, piperazinyl substituted with cyclo(C₄-C₆)alkyl, piperidyl substituted with (C₁-C₄)alkoxy(C₁-C₄)alkoxy, piperidyl substituted
35 with (C₁-C₄)alkoxy(C₄-C₆)alkoxy, piperidyl

substituted with (C₁-C₄)alkoxy(C₄-C₆)alkylthio, and di(C₁-C₄)alkylmorpholino;

benzoyl which has phenyl substituted with a suitable substituent selected from the group consisting of (C₁-C₄)alkoxy having cyclo(C₄-C₆)-alkyl and (C₁-C₄)alkoxycarbonylamino, (C₁-C₄)alkoxy having cyclo(C₄-C₆)alkyl and amino, phenyl having (C₄-C₆)alkoxy, thiazolyl having (C₄-C₆)alkyl, piperazinyl having cyclo(C₄-C₆)alkyl, piperazinyl having phenyl substituted with di(C₁-C₄)-alkylmorpholino, and benzoxazolyl having (C₄-C₆)-alkyl;

benzoyl which has (C₇-C₁₄)alkoxy; thiadiazolylcarbonyl which has pyrazolyl substituted with a suitable substituent selected from the group consisting of (C₇-C₁₄)alkyl, phenyl having (C₄-C₆)alkoxy, and phenyl having piperidyl; piperazinylcarbonyl which has xylyl substituted with (C₁-C₄)alkoxy(C₇-C₁₄)alkoxy; or (C₇-C₁₄)alkanoyl;

R² and R³ are independently hydrogen;

(C₁-C₆)alkyl which may have 1 or 2 suitable substituent(s) selected from the group consisting of amino, carboxy, sulfinic acid group, sulfonic acid group, hydroxy(C₁-C₄)alkylamino which may have hydroxy(C₁-C₄)alkyl, hydroxysulfonyloxy, imino, (C₁-C₄)alkoxy, oxo, cyano(C₂-C₄)alkylidene, (C₁-C₄)alkylthio, and pyrazolyl which may have (C₁-C₄)alkyl;

(C₁-C₄)alkoxycarbonyl which may have (C₁-C₄)alkanoyloxy, dioxacyclo(C₄-C₆)alkenyl which may have oxo, and (C₁-C₄)alkyl;

fluorenyl(C₁-C₄)alkoxycarbonyl;

(C₂-C₄)alkenylloxycarbonyl;

(C₁-C₆)alkanoyl which may have 1 or 2 suitable

substituent(s) selected from the group consisting of amino, hydroxy and pyrazolyl;

pyrrolidinylcarbonyl;

morpholinocarbonyl;

5 mono or di(C₁-C₄)alkylcarbonyl;

sulfonic acid group;

piperidyl which may have 1 or 2 suitable

substituent(s) selected from the group consisting of (C₁-C₄)alkyl, hydroxy(C₁-C₄)alkyl,

10 carboxy(C₁-C₄)alkanoyl which may have amino, and azetidylcarbonyl;

dioxacyclo(C₄-C₆)alkyl which may have 1 or 2 suitable substituent(s) selected from the group consisting of (C₁-C₄)alkyl, and cyclo(C₄-C₆)alkyl;

15 thiopyranyl which may have 1 or 2 oxo;

(C₂-C₄)alkylidene which may have mono or

di(C₁-C₄)alkylamino;

carboxy(C₇-C₁₄)alkyl or

cyano,

20 R⁴ is hydrogen or hydroxy,

R⁵ is hydrogen, hydroxy, (C₁-C₄)alkoxy or hydroxysulfonyloxy, and

R⁶ is hydroxy or (C₂-C₄)alkenyloxy carbonyloxy.

25 Process 1

The object compound (Ia) or a salt thereof can be prepared by reducing a compound (II) or a salt thereof.

Suitable salts of the compounds (Ia) and (II) may be the same as those exemplified for the compound (I).

30 The reaction can be carried out in a conventional manner namely, chemical reduction or catalytic reduction.

Suitable reducing agents to be used in chemical reduction are a combination of metal [e.g. tin, zinc, iron, etc.] or metallic compound [e.g. chromium chloride, chromium
35 acetate, etc.] and an organic or inorganic acid [e.g. formic

acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, hydride transfer reagent such as aluminum hydride compound (e.g. lithium aluminum hydride, lithium tri-tert-butoxyaluminate, etc.), borohydride compound (e.g. sodium borohydride, sodium cyanoborohydride, etc.) or the like etc.].

Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalyst [e.g. platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire, etc.], palladium catalyst [e.g., spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate, etc.], nickel catalyst [e.g. reduced nickel, nickel oxide, Raney nickel, etc.], cobalt catalyst [e.g. reduced cobalt, Raney cobalt, etc.], iron catalyst [e.g. reduced iron, Raney iron, etc.], copper catalyst [e.g. reduced copper, Raney copper, Ullman copper, etc.] or the like.

The reaction of this process is usually carried out in a solvent such as water, alcohol [e.g. methanol, ethanol, propanol, etc.], acetic acid, diethyl ether, dioxane, tetrahydrofuran, methylene chloride, etc. or a mixture thereof.

The reaction is preferably carried out under somewhat milder conditions such as under cooling to warming.

It is included within the scope of the present invention that "hydroxy" in R^4 may be reduced to "hydrogen" during the reaction.

Process 2

The object compound (Ib) or a salt thereof can be prepared by subjecting the compound (Ia) or a salt thereof to protective reaction of amino.

This protective reaction may include acylation or

alkylation reaction of amino and the like, and can be carried out according to a conventional manner such as the one described in Examples or the similar manners thereto.

5 Process 3

The object compound (Id) or a salt thereof can be prepared by subjecting the compound (Ic) or its reactive derivative at the sulfonic acid group or a salt thereof to hydrolysis reaction of the sulfonic acid group.

- 10 The hydrolysis is preferably carried out in the presence of a base or an acid including Lewis acid.

Suitable base may include an inorganic base and an organic base such as an alkali metal [e.g., sodium potassium, etc.], an alkaline earth metal [e.g., magnesium, calcium, etc.], the hydroxide or carbonate or hydrogencarbonate thereof, trialkylamine [e.g. trimethylamine, triethylamine, etc.], picoline, 1,5-diazabicyclo[4.3.0]non-5-ene, or the like.

Suitable acid may include an organic acid [e.g., formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, etc.], and an inorganic acid [e.g., hydrochloric acid, hydrobromic acid, sulfuric acid, hydrogen chloride, hydrogen bromide, etc.].

The elimination using Lewis acid such as trihaloacetic acid [e.g., trichloroacetic acid, trifluoroacetic acid, etc.], or the like preferably carried out in the presence of cation trapping agent [e.g., anisole, phenol, etc.].

The reaction is usually carried out in a conventional solvent such as water, alcohol [e.g. methanol, ethanol, isopropyl alcohol, etc.], tetrahydrofuran, dioxane, toluene, methylene chloride, ethylene dichloride, chloroform, N,N-dimethylformamide, N,N-dimethylacetamide or any other organic solvent which do not adversely affect the reaction, or the mixture thereof.

35 The reaction temperature is not critical and the

reaction is usually carried out under cooling to warming.

Process 4

The object compound (If) or a salt thereof can be
5 prepared by subjecting a compound (Ie) or a salt thereof to elimination reaction of amino protective group.

This reaction is carried out in accordance with a conventional method such as hydrolysis, reduction or the like.

10 The hydrolysis is preferably carried out in the presence of a base or an acid including Lewis acid. Suitable base may include an inorganic base and an organic base such as an alkali metal [e.g. sodium, potassium, etc.], an alkaline earth metal [e.g. magnesium, calcium, etc.], the hydroxide or
15 carbonate or bicarbonate thereof, trialkylamine [e.g. trimethylamine, triethylamine, etc.], picoline, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,4-diazabicyclo[2.2.2]octane, 1,8-diazabicyclo[5.4.0]undec-7-ene, or the like.

Suitable acid may include an organic acid [e.g. formic
20 acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, etc.] and an inorganic acid [e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, hydrogen chloride, hydrogen bromide, etc.]. The elimination using
Lewis acid such as trihaloacetic acid [e.g. trichloroacetic
25 acid, trifluoroacetic acid, etc.] or the like is preferably carried out in the presence of cation trapping agents [e.g. anisole, phenol, etc.].

The reaction is usually carried out in a solvent such as water, an alcohol [e.g. methanol, ethanol, etc.], methylene
30 chloride, tetrahydrofuran, a mixture thereof or any other solvent which does not adversely influence the reaction. A liquid base or acid can be also used as the solvent. The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

35 The reduction method applicable for the elimination

reaction may include chemical reduction and catalytic reduction.

Suitable reducing agents to be used in chemical reduction are a combination of metal [e.g. tin, zinc, iron, etc.] or metallic compound [e.g. chromium chloride, chromium acetate, etc.] and an organic or inorganic acid [e.g. formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, etc.].

Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalysts [e.g. platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire, etc.], palladium catalysts [e.g. spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium, palladium on barium, sulfate, palladium on barium carbonate, etc.], nickel catalysts [e.g. reduced nickel, nickel oxide, Raney nickel, etc.], cobalt catalysts [e.g. reduced cobalt, Raney cobalt, etc.], iron catalysts [e.g. reduced iron, Raney iron, etc.], copper catalysts [e.g. reduced copper, Raney copper, Ullman copper, etc.] and the like.

The reduction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, methanol, ethanol, propanol, N,N-dimethylformamide, or a mixture thereof. Additionally, in case that the above-mentioned acids to be used in chemical reduction are in liquid, they can also be used as a solvent. Further, a suitable solvent to be used in catalytic reduction may be the above-mentioned solvent, and other conventional solvent such as diethyl ether, dioxane, tetrahydrofuran, etc., or a mixture thereof.

The reaction temperature of this reduction is not critical and the reaction is usually carried out under cooling to warming.

Process 5

The compound (I_g) or a salt thereof can be prepared by reducing the compound (II) or a salt thereof, and then reacting with the compound (IV) of the formula:



(wherein R_C^3 is acyl group)
or its reactive derivative, or a salt thereof.

10

Suitable reactive derivative of the compound (IV) may include an acid halide, an acid anhydride, an activated ester, and the like. The suitable example may be an acid chloride; acid azide; a mixed acid anhydride with an acid
15 such as substituted phosphoric acid (e.g., dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc.), dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, alkanesulfonic acid (e.g., methanesulfonic acid,
20 ethanesulfonic acid, etc.), sulfuric acid, alkylcarbonic acid, aliphatic carboxylic acid (e.g., pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid, trichloroacetic acid, etc.); aromatic carboxylic acid (e.g., benzoic acid, etc.); a symmetrical acid anydride; an
25 activated amide with imidazole, 4-substitud imidazole, dimethylpyrazole, triazole or tetrazole; an activated ester (e.g., cyanomethyl, ester methoxymethyl ester, dimethyliminomethyl $[(CH_3)_2\overset{+}{N}=CH-]$ ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl
30 ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenylthioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester, etc.); an ester with a N-hydroxy
35 compound (e.g., N,N-dimethylhydroxylamine,

1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxybenzotriazole, N-hydroxyphthalimide, 1-hydroxy-6-chloro-1H-benzotriazole, etc.); and the like. These reactive derivatives can optionally be selected from
5 them according to the kind of the compound (IV) to be used.

The reaction is usually carried out in a conventional solvent such as water, acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide,
10 pyridine or any other organic solvent which do not adversely affect the reaction, or the mixture thereof.

When the compound (IV) is used in free acid form or its salt form in the reaction, the reaction is preferably carried out in the presence of a conventional condensing agent such
15 as N,N'-dicyclohexylcarbodiimide; N-cyclohexyl-N'-morpholinoethylcarbodiimide); N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide; N,N'-diisopropylcarboximide; N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide; N,N-carbonyl-bis(2-methylimidazole); pentamethyleneketene-N-cyclohexylimine; diphenylketene-N-cyclohexylimine,
20 ethoxyacetylene; 1-alkoxy-1-chloroethylene; trialkyl phosphite; isopropyl polyphosphate; phosphorous oxychloride (phosphoryl chloride); phosphorous trichloride; thionyl chloride; oxalyl chloride; triphenylphosphite;
25 2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl-5-(m-sulfophenyl)isoxazolium hydroxide intra-molecular salt; 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole; so-called Vilsmeier reagent prepared by the reaction of N,N-dimethylformamide with thionyl chloride, phosgene,
30 phosphorous oxychloride, etc.; or the like.

The reaction may also be carried out in the presence of an organic or inorganic base such as an alkali metal bicarbonate, tri(lower)alkylamine (e.g., triethylamine, diisopropylethylamine, etc.), pyridine,
35 di(lower)alkylaminopyridine (e.g., 4-dimethylaminopyridine,

etc.) N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine, or the like.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to heating.

5 Process 6

The object compound (Ii) or a salt thereof can be prepared by reacting the compound (Ih) or a salt thereof with the compound (V) of the formula:



(wherein R_D^2 is acyl group)
or its reactive derivative, or a salt thereof.

15 This reaction can be carried out according to a conventional manner such as the one described in Process 5, Examples or the similar manner thereto.

20 Process 7

The object compound (Ik) or a salt thereof can be prepared by reacting the compound (Ij) or its reactive derivative at the amino group or a salt thereof with the compound (III) or its reactive derivative at the carboxy group or a salt thereof.

Suitable reactive derivative at the carboxy group of the compound (III) may include an acid halide, an acid anhydride, an activated amide, an activated ester, and the like. Suitable examples of the reactive derivatives may be an acid chloride; an acid azide; a mixed acid anhydride with an acid such as substituted phosphoric acid [e.g., dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc.], dialkylphosphorous acid, sulfurous acid, thiosuluric acid, 35 sulfuric acid, sulfonic acid [e.g., methanesulfonic acid,

etc.], aliphatic carboxylic acid [e.g., acetic acid, propionic acid, butyric acid, isobutyric acid, pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid, trichloroacetic acid, etc.];
5 or aromatic carboxylic acid [e.g., benzoic acid, etc.]; a symmetrical acid anhydride; an activated amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole, tetrazole or 1-hydroxy-1H-benzotriazole; or an activated ester [e.g., cyanomethyl ester, methoxymethyl
10 ester, dimethyliminomethyl $[(CH_3)_2N^+=CH-]$ ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachloropentyl ester, mesylphenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl
15 thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester, etc.], or an ester with a N-hydroxy compound [e.g. N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxyphthalimide, 1-hydroxy-1H-benzotriazole, etc.], and the like. These
20 reactive derivatives can optionally be selected from them according to the kind of the compound (III) to be used.

Suitable salts of the compound (III) and its reactive derivative can be referred to the ones as exemplified for the object compound (I).

25 The reaction is usually carried out in a conventional solvent such as water, alcohol [e.g., methanol, ethanol, etc.], acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent
30 which does not adversely influence the reaction. These conventional solvents may also be used in a mixture with water.

In this reaction, when the compound (III) is used in a free acid form or its salt form, the reaction is preferably
35 carried out in the presence of a conventional condensing

- agent such as N,N'-dicyclohexylcarbodiimide;
N-cyclohexyl-N'-morpholinoethylcarbodiimide;
N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide;
N,N'-diethylcarbodiimide; N,N'-diisopropylcarbodiimide;
- 5 N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide;
N,N-carbonylbis-(2-methylimidazole);
pentamethyleneketene-N-cyclohexylimine;
diphenylketene-N-cyclohexylimine, ethoxyacetylene;
1-alkoxy-2-chloroethylene; trialkyl phosphite;
- 10 ethyl polyphosphate; isopropyl polyphosphate;
phosphorus oxychloride (phosphoryl chloride);
phosphorus trichloride; thionyl chloride; oxalyl chloride;
lower alkyl haloformate [e.g., ethyl chloroformate, isopropyl
chloroformate, etc.]; triphenylphosphine;
- 15 2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl-5-(m-
sulfophenyl)isoxazolium hydroxide intramolecular salt;
1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole;
so-called Vilsmeier reagent prepared by the reaction of N,N-
dimethylformamide with thionyl chloride, phosgene,
- 20 trichloromethyl chloroformate, phosphorous oxychloride,
methanesulfonyl chloride, etc.; or the like.

The reaction may also be carried out in the presence of
an inorganic or organic base such as an alkali metal
carbonate alkali metal bicarbonate, tri(lower)alkylamine
25 (e.g., triethylamine, diisopropylethylamine, etc.), pyridine,
di(lower)alkylaminopyridine (e.g., 4-dimethylaminopyridine,
etc.), N-(lower)alkylmorpholine, N,N-
di(lower)alkylbenzylamine, or the like.

- The reaction temperature is not critical, and the
30 reaction is usually carried out under cooling to warming.

Process A

The object compound (IIa) or a salt thereof can be prepared by reacting the compound (IIB) or its reactive derivative at the amino group or a salt thereof with the compound (III) or its reactive derivative at the carboxy group or a salt thereof.

Suitable reactive derivative at the carboxy group of the compound (III) may include an acid halide, an acid anhydride, an activated amide, an activated ester, and the like.

Suitable examples of the reactive derivatives may be an acid chloride; an acid azide; a mixed acid anhydride with an acid such as substituted phosphoric acid [e.g., dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc.], dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, sulfuric acid, sulfonic acid [e.g., methanesulfonic acid, etc.], aliphatic carboxylic acid [e.g., acetic acid, propionic acid, butyric acid, isobutyric acid, pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid trichloroacetic acid, etc.]; or aromatic carboxylic acid [e.g., benzoic acid, etc.]; a symmetrical acid, anhydride; an activated amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole, tetrazole or 1-hydroxy-1H-benzotriazole; or an activated ester [e.g., cyanomethyl ester, methoxymethyl ester, dimethyliminomethyl $[(CH_3)_2N=CH-]$ ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachloropentyl ester, mesylphenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester, etc.], or an ester with a N-hydroxy compound [e.g. N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxyphthalimide, 1-hydroxy-1H-benzotriazole, etc.], and the like. These reactive

derivatives can optionally be selected from them according to the kind of the compound (III) to be used.

Suitable salts of the compound (III) and its reactive derivative can be referred to the ones as exemplified for the
5 object compound (I).

The reaction is usually carried out in a conventional solvent such as water, alcohol [e.g., methanol, ethanol, etc.], acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate,
10 N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely influence the reaction. These conventional solvent may also be used in a mixture with water.

In this reaction, when the compound (III) is used in a
15 free acid form or its salt form, the reaction is preferably carried out in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide; N-cyclohexyl-N'-morpholinoethylcarbodiimide; N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide;
20 N,N'-diethylcarbodiimide; N,N'-diisopropylcarbodiimide; N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide; N,N-carbonylbis-(2-methylimidazole); pentamethyleneketene-N-cyclohexylimine; diphenylketene-N-cyclohexylimine, ethoxyacetylene;
25 1-alkoxy-2-chloroethylene; trialkyl phosphite; ethyl polyphosphate; isopropyl polyphosphate; phosphorus oxychloride (phosphoryl chloride); phosphorus trichloride; thionyl chloride; oxalyl chloride; lower alkyl haloformate [e.g., ethyl chloroformate, isopropyl
30 chloroformate, etc.]; triphenylphosphine; 2-ethyl-7-hydroxybenzisoaxazolium salt; 2-ethyl-5-(m-sulfophenyl)isoxazolium hydroxide intramolecular salt; 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole; so-called Vilsmeier reagent prepared by the reaction of
35 N,N-dimethylformamide with thionyl chloride, phosgene,

trichloromethyl chloroformate, phosphorous oxychloride, methanesulfonyl chloride, etc.; or the like.

The reaction may also be carried out in the presence of an inorganic or organic base such as an alkali metal carbonate, alkali metal bicarbonate, tri(lower)alkylamine (e.g., triethylamine, diisopropylethylamine, etc.), pyridine, di(lower)alkylaminopyridine (e.g., 4-dimethylaminopyridine, etc.), N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine, or the like.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to warming.

The compounds obtained by the above Processes 1 to 7 and Process A can be isolated and purified by a conventional method such as pulverization, recrystallization, column-chromatography, high-performance liquid chromatography (HPLC), reprecipitation, desalting resin column chromatography, or the like.

The compounds obtained by the above Processes 1 to 7 and Process A may be obtained as its solvate, such as hydrate, and its solvate, such as hydrate is included within the scope of the present invention.

It is to be noted that each of the object compound (I) may include one or more stereoisomer such as optical isomer(s) and geometrical isomer(s) due to asymmetric carbon atom(s) and double bond(s) and all such isomers and the mixture thereof are included within the scope of the present invention.

The object compound (I) or a salt thereof may include solvated compound [e.g., enclosure compound (e.g., hydrate, etc.)].

The object compound (I) or a salt thereof may include both its crystal form and non-crystal form.

It should be understood that the compounds in the present invention may include the prodrug form.

The patent applications and publications cited herein are incorporated by reference.

Biological property of the polypeptide
compound (I) of the present invention

In order to show the usefulness of the polypeptide compound (I) of the present invention, the biological data of the representative compound is explained in the following.

10 Test (Antimicrobial activity):

In vitro antimicrobial activity of the object compound of Example 5 disclosed later was determined by MIC_s in mouse serum as described below.

15 Test Method:

The MIC_s in mouse serum were determined by the microdilution method using ICR mouse serum buffered with 20 mM HEPES buffer (pH 7.3) as a test medium. Inoculum suspension of 10⁶ cells/ml were prepared by a hemocytometric procedure and diluted to obtain an inoculum size of approximately 1.0 x 10³ cells/ml. Microplates were incubated at 37°C for 24 hours in 5% CO₂. The MIC_s were defined as the lowest concentrations at which no visible growth was observed.

25

Test Result:

MIC (μg/ml)

Test compound Test organism	The object compound of <u>Example 5</u>
Candida albicans FP-633	<0.3

30

From the test result, it is realized that the object compound (I) of the present invention has an antimicrobial activity (especially, antifungal activity).

35

In more details, the object compound (I) of the present invention have an antifungal activity, particularly against the following fungi.

5

Acremonium;

Absidia (e.g., *Absidia corymbifera*, etc);

Aspergillus (e.g., *Aspergillus clavatus*, *Aspergillus flavus*,

10 *Aspergillus fumigatus*, *Aspergillus nidulans*, *Aspergillus niger*, *Aspergillus terreus*, *Aspergillus versicolor*, etc);

Blastomyces (e.g., *Blastomyces dermatitidis*, etc);

Candida (e.g., *Candida albicans*, *Candida glabrata*, *Candida guilliermondii*, *Candida kefyr*, *Candida krusei*, *Candida parapsilosis*, *Candida stellatoidea*, *Candida tropicalis*,

15 *candida utilis*, etc.);

Cladosporium (e.g., *Cladosporium trichloides*, etc);

Coccidioides (e.g., *Coccidioides immitis*, etc);

Cryptococcus (e.g., *Cryptococcus neoformans*, etc);

Cunninghamella (e.g., *Cunninghamella elegans*, etc);

20 *Dermatophyte*;

Exophiala (e.g., *Exophiala dermatitidis*, *Exophiala spinifera*, etc);

Epidermophyton (e.g., *Epidermophyton floccosum*, etc);

Fonsecaea (e.g., *Fonsecaea pedrosoi*, etc);

25 *Fusarium* (e.g., *Fusarium solani*, etc);

Geotrichum (e.g., *Geotrichum candidum*, etc);

Histoplasma (e.g., *Histoplasma capsulatum* var. *capsulatum*, etc).

Malassezia (e.g., *Malassezia furfur*, etc);

30 *Microsporum* (e.g., *Microsporum canis*, *Microsporum gypseum*, etc);

Mucor;

Paracoccidioides (e.g., *Paracoccidioides brasiliensis*, etc);

Penicillium (e.g., *Penicillium marneffeii*, etc);

35 *Phialophora*;

- Pneumocystis* (e.g., *Pneumocystis carinii*, etc);
Pseudallescheria (e.g., *Pseudallescheria boydii*, etc);
Rhizopus (e.g., *Rhizopus microsporus* var. *rhizopodiformis*,
Rhizopus oryzae, etc);
- 5 *Saccharomyces* (e.g., *Saccharomyces cerevisiae*, etc);
Scopulariopsis;
Sporothrix (e.g., *Sporothrix schenckii*, etc);
Trichophyton (e.g., *Trichophyton mentagrophytes*, *Trichophyton*
rubrum, etc);
- 10 *Trichosporon* (e.g., *Trichosporon asahii*, *Trichosporon*
cutaneum, etc).

- The above fungi are well-known to cause various
infection diseases in skin, hair, nail, oral mucosa,
15 gastrointestinal tract, bronchus, lung, endocardium, brain,
meninges, urinary organ, vaginal protion, oral cavity,
ophthalmus, systemic, kidney, bronchus, heart, external
auditory canal, bone, nasal cavity, paranasal cavity, spleen,
liver, hypodermal tissue, lymph doct, gastrointestinal,
20 articulation, muscle, tendon, interstitial plasma cell in
lung, and so on.

- Therefore, the object compound (I) of the present
invention are useful for preventing and treating various
25 infectious diseases, such as dermatophytosis (e.g.,
trichophytosis, etc), pityriasis versicolor, candidiasis,
cryptococcosis, geotrichosis, trichosporosis, aspergillosis,
penicilliosis, fusariosis, zygomycosis, sporotrichosis,
chromomycosis, coccidioidomycosis, histoplasmosis,
30 blastomycosis, paracoccidioidomycosis, pseudallescheriosis,
mycetoma, mycotic keratitis, otomycosis, pneumocystosis, and
so on.

- The pharmaceutical composition of the present invention
35 can be used in the form of a pharmaceutical preparation, for

example, in solid, semisolid or liquid form, which contains the object compound (I) or a pharmaceutically acceptable salt thereof, as an active ingredient in admixture with an organic or inorganic carrier or excipient which is suitable for
5 rectal; pulmonary (nasal or buccal inhalation); ocular; external (topical); oral administration; parenteral (including subcutaneous, intravenous and intramuscular) administrations; insufflation (including aerosols from metered dose inhalator); nebulizer; or dry powder inhalator.

10 The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers in a solid form such as granules, tablets, dragees, pellets, troches, capsules, or suppositories; creams; ointments; aerosols; powders for insufflation; in a liquid
15 form such as solutions, emulsions, or suspensions for injection; ingestion; eye drops; and any other form suitable for use. And, if necessary, there may be included in the above preparation auxiliary substance such as stabilizing, thickening, wetting, emulsifying and coloring agents;
20 perfumes or buffer; or any other commonly may be used as additives.

The object compound (I) or a pharmaceutically acceptable salt thereof is/are included in the pharmaceutical composition in an amount sufficient to produce the desired
25 antimicrobial effect upon the process or condition of diseases.

For applying the composition to humans, it is preferable to apply it by intravenous, intramuscular, pulmonary, oral administration, eye drop administration or insufflation.

30 While the dosage of therapeutically effective amount of the object compound (I) varies from and also depends upon the age and condition of each individual patient to be treated, in the case of intravenous administration, a daily dose of 0.01-20 mg of the object compound (I) per kg weight of human being
35 in the case of intramuscular administration, a daily dose of

0.1-20 mg of the object compound (I) per kg weight of human being, in case of oral administration, a daily dose of 0.5-50 mg of the object compound (I) per kg weight of human being is generally given for treating or preventing infectious diseases.

Especially in case of the treatment or prevention of Pneumocystis carinii infection, the followings are to be noted.

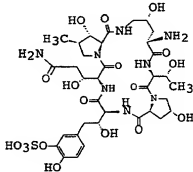
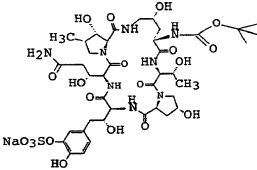
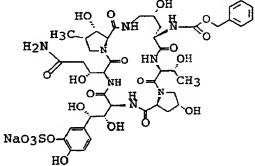
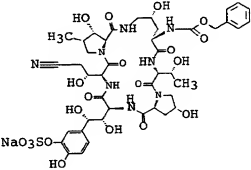
For administration by inhalation, the compounds of the present invention are conveniently delivered in the form of an aerosol spray presentation form pressurized as powders which may be formulated and the powder compositions may be inhaled with the aid of an insufflation powder inhaler device. The preferred delivery system for inhalation is a metered dose inhalation aerosol, which may be formulated as a suspension or solution of compound in suitable propellants such as fluorocarbons or hydrocarbons.

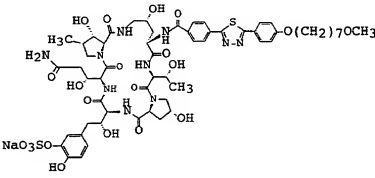
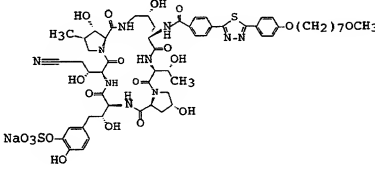
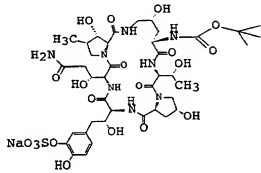
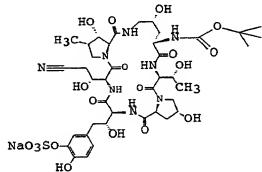
Because of desirability to directly treat lung and bronchi, aerosol administration is a preferred method of administration. Insufflation is also a desirable method, especially where infection may have spread to ears and other body cavities.

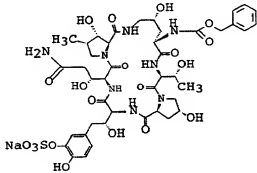
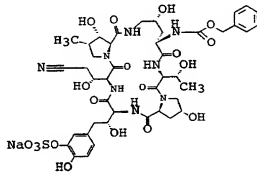
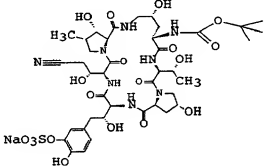
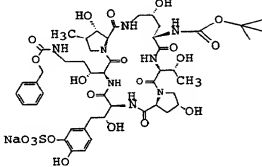
Alternatively, parenteral administration may be employed using drip intravenous administration.

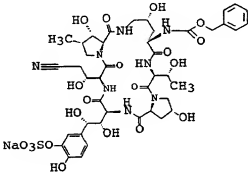
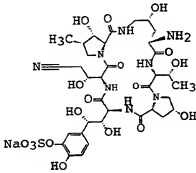
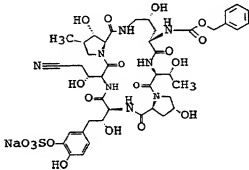
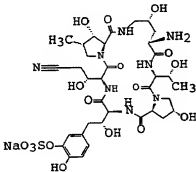
The following Preparations and Examples are given for the purpose of illustrating the present invention in more detail.

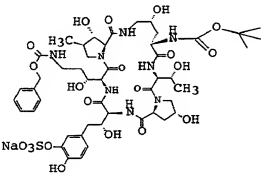
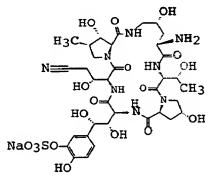
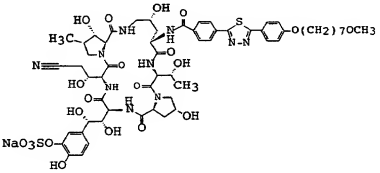
The Starting Compounds used and the Object Compounds obtained in the following Preparations 1 to 23 are given in the table as below, in which the formulas of the starting compounds are in the upper column and the formulas of the object compounds are in the lower column, respectively.

Preparation No.	Formula
1	
	
2	
	

Preparation No.	Formula
3	
	
4	
	

Preparation No.	Formula
5	
	
6	
	

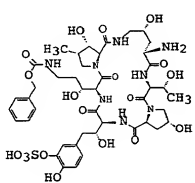
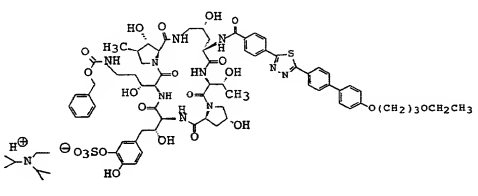
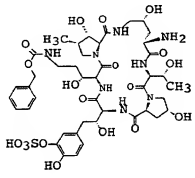
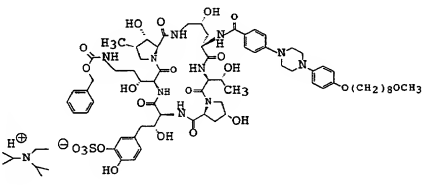
Preparation No.	Formula
7	
	
8	
	

Preparation No.	Formula
9	
10	 

Preparation No.	Formula
11 ↓ 21	

Preparation No.	R	X
11		Na
12		Na
13		Na

Preparation No.	R	X
14		Na
15		
16		
17		Na
18		
19		Na
20		Na
21		Na

Preparation No.	Formula
22	
	
23	
	

Preparation 1

A solution of starting compound (20 g) in 1,4-dioxane (100 ml) was treated with a solution of 1N-sodium hydroxide (44.2 ml) diluted to 100 ml with water, and to the stirred mixture was added a solution of di-tert-butylidicarbonate (9.2 g) in 1,4-dioxane (50 ml) and then stirred for 2 hours at room temperature. 500 ml of pH 6.86 phosphate buffer and 100 ml ethyl acetate were added and the mixture was stirred and the organic layer discarded. The aqueous layer was adjusted to pH 7.0 with 1N-hydrochloric acid then evaporated to remove organic solvent, filtered, and purified by ODS column chromatography eluting with aqueous methanol (5-15%). Object compound containing fractions were pooled, evaporated, and lyophilized to give object compound (19.61 g) as an amorphous white powder.

NMR (DMSO- d_6 , δ): 0.95 (3H, d, $J=6.8\text{Hz}$), 1.07 (3H, d, $J=5.5\text{Hz}$), 1.34 (9H, s), 1.40-2.50 (9H, m), 2.80-3.0 (1H, m), 3.4-4.5 (15H, m), 4.70-5.40 (8H, m), 6.60-7.05 (6H, m), 7.25-8.00 (5H, m), 8.71 (1H, s)

MASS (m/z): 1003.3 (M^+-1)

Preparation 2

A mixture of starting compound (500 mg), N,N-dimethylformamide (5 ml) and synthetic A-4 zeolite (500 mg, Wako Chemical) was treated with diisopropyl ethylamine (66 mg), followed by methanesulfonyl chloride (58.5 mg) dropwise. After 1 hour at room temperature, further diisopropyl ethylamine (66 mg) and methanesulfonyl chloride (58.5 mg) were added. After 1.5 hours, additional diisopropylamine (66 mg) and methanesulfonyl chloride (58.5 mg) were added. After 1.5 hours, the mixture was filtered and the filtrate was poured into ethyl acetate. The precipitate was collected, washed with ethyl acetate and dried. The powder was dissolved in saturated sodium hydrogen carbonate solution then purified by ODS column chromatography

(Daisogel SP-120 ODS Daiso) eluting with aqueous methanol (5-12.5%). Object compound-containing fractions were pooled, evaporated to remove methanol, and lyophilized to give object compound (210 mg) as an amorphous white powder.

- 5 IR (KBr): 2258.2, 1664.3, 1629.6, 1529.3, 1517.7,
1446.4, 1268.9 cm^{-1}
- NMR (DMSO- d_6 , δ): 0.94 (3H, d, $J=6.7\text{Hz}$), 1.07 (3H, d, $J=5\text{Hz}$), 1.40-3.00 (9H, m), 3.10-4.50 (15H, m),
4.50-5.30 (10H, m), 5.66-5.69 (1H, m), 6.73 (1H, d, $J=8.2\text{Hz}$), 6.82 (1H, d, $J=8\text{Hz}$), 7.05 (1H, d, $J=1.7\text{Hz}$), 7.33 (5H, s), 7.20-7.50 (3H, m), 7.6-7.7 (1H, m), 8.27 (1H, d, $J=8.3\text{Hz}$), 8.84 (1H, s)
- 10 MASS (m/z): 1081.3 ($\text{M}^+ + \text{Na}$)
- Elemental Analysis Calcd. for $\text{C}_{43}\text{H}_{55}\text{N}_8\text{O}_{20}\text{SNa} \cdot 6\text{H}_2\text{O}$:
15 C 44.25, H 5.79, N 9.60
Found: C 44.30, H 5.79, N 9.48

The following compounds [Preparations 3 to 5] were obtained according to a similar manner to that of Preparation

20 2.

Preparation 3

- IR (KBr): 2256.3, 1631.5, 1538.9, 1513.8, 1442.5,
1257.4 cm^{-1}
- 25 NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.7\text{Hz}$), 1.12 (3H, d, $J=5.5\text{Hz}$), 1.20-1.60 (8H, m), 1.65-3.05 (13H, m),
3.21 (3H, s), 3.30 (2H, t, $J=6.4\text{Hz}$), 3.45-4.57 (16H, m), 4.70-5.30 (7H, m), 5.87 (1H, d, $J=6.1\text{Hz}$),
6.72 (1H, d, $J=8.2\text{Hz}$), 6.76-6.81 (1H, m), 6.98 (1H, d, $J=1.3\text{Hz}$), 7.13 (2H, d, $J=8.8\text{Hz}$), 7.40-7.53 (2H, m), 7.79 (1H, br s), 7.98 (2H, d, $J=8.7\text{Hz}$), 8.10 (4H, s), 8.34 (1H, d, $J=7.9\text{Hz}$), 8.72 (1H, d, $J=5.7\text{Hz}$), 8.73 (1H, s)
- 30 MASS (m/z): 1293.4 ($\text{M}^+ - \text{Na}$)
- 35 Elemental Analysis Calcd. for $\text{C}_{58}\text{H}_{73}\text{N}_{10}\text{O}_{20}\text{SNa} \cdot 6\text{H}_2\text{O}$:

C 48.87, H 6.01, N 9.83

Found: C 48.69, H 6.09, N 9.70

Preparation 4

- 5 IR (KBr): 2256.3, 1666.2, 1631.5, 1535.1, 1515.8,
1448.3, 1442.5, 1272.8, 1251.6, 1166.7, 1083.8,
1047.2 cm^{-1}
- NMR (DMSO- d_6 , δ): 0.95 (3H, d, $J=6.7\text{Hz}$), 1.09 (3H, d,
 $J=5.1\text{Hz}$), 1.35 (9H, s), 1.50-3.00 (9H, m), 3.10-
10 4.50 (17H, m), 4.65-5.00 (5H, m), 5.15-5.17 (2H,
m), 5.70-5.90 (1H, m), 6.68-6.78 (2H, m), 6.86-6.96
(2H, m), 7.32 (1H, d, $J=8\text{Hz}$), 7.40-7.50 (1H, m),
7.70-7.80 (1H, m), 8.30-8.40 (1H, m), 8.72 (1H, s)
- MASS (m/z): 985.3 (M^+ -Na)
- 15 Elemental Analysis Calcd. for $\text{C}_{40}\text{H}_{58}\text{N}_8\text{O}_{19}\text{SNa}\cdot 9\text{H}_2\text{O}$:
C 41.02, H 6.45, N 9.57
Found: C 41.35, H 6.42, N 9.61

Preparation 5

- 20 IR (KBr): 2256.3, 1668.1, 1648.8, 1631.5, 1538.9,
1513.8, 1454.1, 1267.0 cm^{-1}
- NMR (DMSO- d_6 , δ): 0.95 (3H, d, $J=6.8\text{Hz}$), 1.07 (3H, d,
 $J=5.2\text{Hz}$), 1.5-2.9 (10H, m), 3.2-4.5 (15H, m), 4.7-
5.2 (9H, m), 5.7-5.8 (1H, m), 6.60-6.78 (2H, m),
25 6.96 (1H, br s), 7.33 (5H, s), 7.2-7.5 (3H, m),
7.7-7.8 (1H, m), 8.3 (1H, d, $J=7.5\text{Hz}$), 8.73 (1H, br
s)
- MASS (m/z): 1065.2 (M^+ +Na)
- Elemental Analysis Calcd. for $\text{C}_{43}\text{H}_{55}\text{N}_8\text{O}_{19}\text{SNa}\cdot 7\text{H}_2\text{O}$:
30 C 44.18, H 5.95, N 9.58
Found: C 44.21, H 5.82, N 9.54

Preparation 6

- A solution of starting compound (2.0 g) in methanol (100
35 ml) - water (20 ml) was treated with cobalt(II) chloride

hexahydrate (1.89 g) and then stirred to give a pink solution. Sodium borohydride (1.5 g) was then added portionwise and then stirred for 1 hour at room temperature. The reaction mixture was filtered through a bed of celite, washing with methanol (100 ml) - water (30 ml) solution. The ice-cooled filtrate was then treated dropwise with a solution of benzyloxy carbonyl chloride (Z-chloride) (0.34 ml) in tetrahydrofuran (5 ml) and stirred for 1 hour at the same temperature. Ethyl acetate (50 ml) was added followed by water (200 ml) and after stirring ~ 5 minutes, the separated organic layer was discarded. The aqueous layer was adjusted to pH 8.8 and evaporated to remove organic solvent and then purified by ODS column chromatography, eluting with aqueous acetonitrile (10-30%). Object compound containing fractions were pooled, evaporated, and lyophilized to give object compound (1.61 g) as an amorphous white powder.

IR (KBr): 1666.2, 1631.5, 1517.7, 1444.4, 1267.0 cm^{-1}

NMR (DMSO- d_6 , δ): 0.94 (3H, d, $J=6.7\text{Hz}$), 1.00-1.15 (3H, m), 1.33 (9H, s), 1.35-2.10 (6H, m), 2.10-2.50 (4H, m), 2.80-3.30 (4H, m), 3.60-4.55 (12H, m), 4.60-4.90 (2H, m), 4.99 (2H, s), 4.50-5.30 (4H, m), 6.60-7.10 (4H, m), 7.33 (5H, s), 7.35-7.90 (3H, m), 8.72 (1H, br s)

MASS (m/z): 1123.3 (M^+ -Na)

Elemental Analysis Calcd. for $\text{C}_{48}\text{H}_{67}\text{N}_8\text{O}_{21}\text{SNa}\cdot 6\text{H}_2\text{O}$:

C 45.93, H 6.34, N 8.93

Found: C 45.68, H 6.33, N 8.82

Preparation 7

A solution of starting compound (2.0 g) in methanol (30 ml) was treated with wet 10% palladium on carbon (1.5 g) and exposed to one atmosphere of hydrogen gas via balloon. After 5.5 hours, water (4 ml) was added and hydrogenation continued for a further 30 minutes. Methanol (100 ml) was added and the catalyst removed by filtration. The solution was

concentrated in vacuo to remove methanol and the aqueous residue lyophilized to give object compound (1.69 g) as a pink colored amorphous powder.

IR (KBr): 2256.3, 1648.8, 1631.5, 1538.9, 1515.8,

5 1440.6, 1083.8, 1047.2 cm^{-1}

NMR (DMSO- d_6 , δ): 0.94 (3H, d, $J=6.7\text{Hz}$), 1.09 (3H, d, $J=5.9\text{Hz}$), 1.7-2.8 (10H, m), 3.0-4.5 (19H, m), 4.6-5.3 (6H, m), 5.85-6.0 (1H, m), 6.72 (1H, d, $J=8.2\text{Hz}$), 6.82 (1H, dd, $J=1.8$ and 8.4Hz), 7.06 (1H, d, $J=1.7\text{Hz}$), 7.32 (1H, d, $J=8.9\text{Hz}$), 7.44 (1H, d, $J=9.1\text{Hz}$), 7.6-7.8 (2H, m), 7.8-8.0 (1H, br s)

10 MASS (m/z): 901.2 ($M^+-\text{Na}$)

Elemental Analysis Calcd. for $\text{C}_{35}\text{H}_{49}\text{N}_8\text{O}_{18}\text{SNa}\cdot 6\text{H}_2\text{O}$:

C 40.70, H 5.95, N 10.85

15 Found: C 40.60, H 5.94, N 10.71

The following compound was obtained according to a similar manner to that of Preparation 7.

20 Preparation 8

IR (KBr): 2256.3, 1648.8, 1631.5, 1538.9, 1513.8,

1267.0, 1083.8, 1047.2 cm^{-1}

NMR (DMSO- d_6 , δ): 0.96 (3H, d, $J=6.7\text{Hz}$), 1.08 (3H, d, $J=5.9\text{Hz}$), 1.7-2.1 (2H, m), 2.1-2.9 (7H, m), 3.1-4.6 (16H, m), 4.7-5.4 (6H, m), 6.1 (1H, br s), 6.70 (1H, d, $J=8.2\text{Hz}$), 6.75 (1H, d, $J=8.2\text{Hz}$), 6.96 (1H, br s), 7.2-7.55 (2H, m), 7.6-7.9 (2H, m)

25 MASS (m/z): 885.3 ($M^+-\text{Na}$)

Elemental Analysis Calcd. for $\text{C}_{35}\text{H}_{49}\text{N}_8\text{O}_{17}\text{SNa}\cdot 6\text{H}_2\text{O}$:

30 C 41.34, H 6.05, N 11.02

Found: C 41.58, H 5.99, N 10.94

Preparation 9

A suspension of starting compound (1.6 g) in
35 dichloromethane (41 ml) was stirred with cooling at 5°C and

treated with triethylsilane (1.1 ml), followed by trifluoroacetic acid (5.3 ml) dropwise over 30 minutes. After warming to room temperature, the clear solution was stirred for 2 hours, then poured into 450 ml of pH 6.86 phosphate buffer and adjusted to pH 8.5 with 4N-sodium hydroxide solution. Organic solvent was removed by evaporation and the remaining aqueous solution purified by ODS column chromatography, eluting with aqueous acetonitrile (5-20%). Object compound-containing fractions were pooled, evaporated, and lyophilized to give object compound (1.25 g) as an amorphous white powder.

IR (KBr): 1633.4, 1537.0, 1517.7, 1440.6, 1267.0 cm^{-1}

NMR (DMSO-d_6 , δ): 0.95 (3H, d, $J=6.7\text{Hz}$), 1.12 (3H, d, $J=5.8\text{Hz}$), 1.27 (2H, d, $J=6.6\text{Hz}$), 1.28-1.70 (2H, m), 1.75-2.45 (4H, m), 2.65-3.30 (5H, m), 3.50-4.50 (11H, m), 4.60-4.90 (2H, m), 5.00 (2H, s), 5.05-5.40 (5H, m), 6.70 (2H, d, $J=8.2\text{Hz}$), 6.76 (2H, d, $J=8.2\text{Hz}$), 6.96 (1H, s), 7.00-7.15 (1H, m), 7.34 (5H, s), 7.40-7.95 (3H, m), 8.60-8.90 (1H, m)

MASS (m/z): 1023.3 (M^+-1)

Elemental Analysis Calcd. for $\text{C}_{43}\text{H}_{60}\text{N}_8\text{O}_{19}\text{S}_6\text{H}_2\text{O}$:

C 45.58, H 6.40, N 9.89

Found: C 45.49, H 6.24, N 9.70

25 Preparation 10

A solution of starting compound (3 g) in N,N-dimethylformamide (60 ml) was treated with 4-[5-[4-(7-methoxy-n-heptyloxy)phenyl]-1,3,4-thiadiazol-2-yl]benzoic acid benzotriazol-1-yl ester (2.65 g) and diisopropylethylamine (0.564 ml) and stirred for 4 hours 20 minutes at room temperature. Ethyl acetate (1 l) was added and the resulting precipitate collected, washed with isopropyl ether, and dried to give object compound (5.62 g) as a crude powder, which was used directly in the next step without purification.

The following compounds [Preparations 11 to 17] were obtained according to a similar manner to that of Preparation 10.

5

Preparation 11

The object compound was used directly in the next reaction without purification.

10 Preparation 12

The object compound was used directly in the next reaction without purification.

Preparation 1315 MASS (m/z): 1299.3 (M^+ -Na)Preparation 14

The object compound was used directly in the next reaction without purification.

20

Preparation 15

The object compound was used directly in the next reaction without purification.

25 Preparation 16

The object compound was used directly in the next reaction without purification.

Preparation 1730 MASS (m/z): 1237.3 (M^+ -Na)Preparation 18

A mixture of 4-[2-(4-pentyloxyphenyl)imidazo[2,1-b]-[1,3,4]thiadiazol-6-yl]benzoic acid (1.44 g),
35 1-hydroxybenzotriazole (714 mg), diisopropyl ethylamine (0.58

ml) and 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (810 mg) in N,N-dimethylformamide (50 ml) was stirred 6 hours at room temperature, then treated with starting compound (2 g) and stirred overnight. Additional
5 N,N-dimethylformamide (20 ml) was added and stirring continued for a further 5.5 hours. The clear solution was poured into ethyl acetate (1 l) and the precipitate collected and washed with isopropyl ether and dried to give crude
10 object compound (3.58 g), which was used directly in the next step without purification.

The following compounds [Preparations 19 and 20] were obtained according to a similar manner to that of Preparation 18.

15 Preparation 19

MASS (m/z): 1286.3 (M^+ -Na)

20 Preparation 20

MASS (m/z): 1354.4 (M^+ -Na)

The following compound was obtained according to a similar manner to that of Preparation 18.

25 Preparation 21

IR (KBr): 1648.8, 1631.5, 1537.0, 1513.8, 1456.0 cm^{-1}

NMR (DMSO- d_6 , δ): 0.96 (3H, d, $J=7\text{Hz}$), 1.10 (3H, d, $J=5.6\text{Hz}$), 1.18 (6H, d, $J=6\text{Hz}$), 1.4-5.3 (38H, m, 5.88 (1H, d, $J=6\text{Hz}$), 6.71 (1H, d, $J=8\text{Hz}$), 6.75-6.80
30 (1H, m), 6.97 (1H, br s), 7.12 (2H, d, $J=9\text{Hz}$), 7.42 (1H, d, $J=7.6\text{Hz}$), 7.50 (1H, d, $J=9\text{Hz}$), 7.78 (2H, d, $J=8.8\text{Hz}$), 7.7-8.0 (1H, br s), 7.96 (4H, s), 8.32 (1H, d, $J=8\text{Hz}$), 8.50 (1H, d, $J=7.1\text{Hz}$), 8.72 (1H, s), 8.79 (1H, s)

35 MASS (m/z): 1301.4 (M^+ -Na)

The following compounds [Preparations 22 to 23] were obtained according to a similar manner to that of Preparation 10.

5

Preparation 22

NMR (DMSO-d₆, δ): 0.95 (3H, d, J=6.6Hz), 6.67 (1H, d, J=6.9Hz), 6.73-6.75 (1H, m), 6.96 (1H, br s), 7.07 (2H, d, J=8.8Hz), 7.32 (5H, s), 7.73 (2H, d, J=8.7Hz), 7.87 (2H, d, J=8.5Hz), 8.06-8.14 (6H, m), 8.72 (1H, s), 8.80 (1H, d, J=7.1Hz)

10

MASS (m/z): 1465.5 (M⁺-Na)

Preparation 23

15

The object compound was used directly in the next reaction without purification.

Preparation 24

20

To a solution of 1-(tert-butoxycarbonyl)-4-hydroxypiperidine (6 g) in N,N-dimethylformamide (30 ml) was portionwise added sodium hydride (60%, 1.6 g) at 5°C with stirring. The mixture was stirred at room temperature for 0.5 hour and at 60°C for an hour. To the reaction mixture was added dropwise 1,4-dibromobutane (19 g) at 5°C with

25

stirring. The mixture was stirred at room temperature for 4 hours and at 50°C for 2 hours. The reaction mixture was poured into ice-water and extracted with a mixture of ethyl acetate and tetrahydrofuran (1:1). The organic layer was washed with saturated sodium chloride aqueous solution and

30

dried over magnesium sulfate. The magnesium sulfate was filtered under reduced pressure, and the filtrate was concentrated under reduced pressure to give oil. The oil was subjected to column chromatography on silica gel (silica gel 60 F254, Merck) and eluted with a mixture of ethyl acetate

35

and n-hexane (1:10-1:3). The fractions containing the

objective compound were combined and concentrated under reduced pressure to give 1-(tert-butoxycarbonyl)-4-[(4-bromo)butoxy]piperidine (1.5 g).

NMR (CDCl₃, δ): 1.41 (9H, s), 1.43-1.60 (2H, m), 1.65-1.80 (4H, m), 1.85-2.3 (2H, m), 3.02-3.20 (2H, m), 3.38-3.51 (4H, m), 3.68-3.80 (2H, m)
MASS (m/z): 238 (M⁺-Boc-2)

Preparation 25

The mixture of 1-(tert-butoxycarbonyl)-4-[4-(bromobutoxy)]piperidine (3 g) and 28% sodium methoxide in methanol solution (20 ml) in methanol (50 ml) was refluxed for 8.5 hours with stirring. The reaction mixture was concentrated under reduced pressure, added water to the residue and adjusted to pH 4 using the hydrochloric acid. The mixture was extracted with a mixture of ethyl acetate and tetrahydrofuran (1:1), washed with saturated sodium chloride aqueous solution and dried over magnesium sulfate. The magnesium sulfate was filtered by suction, and the filtrate was concentrated under reduced pressure to give an oil. The oil was subjected to column chromatography on silica gel (silica gel 60 F254, Merck) and eluted with a mixture of ethyl acetate and n-hexane (1:5-1:3). The fractions containing the objective compound were combined and concentrated under reduced pressure to give 1-(tert-butoxycarbonyl)-4-(4-methoxybutoxy)piperidine (2.2 g).

NMR (CDCl₃, δ): 1.40 (9H, s), 1.43-1.60 (2H, m), 1.6-1.70 (4H, m), 1.76-1.85 (2H, m), 3.01-3.15 (2H, m), 3.33 (3H, s), 3.36-3.50 (5H, m), 3.69-3.80 (2H, m)

MASS (m/z): 188 (M⁺-Boc+1)

Preparation 26

To a mixture of 1-(tert-butoxycarbonyl)-4-[4-methoxybutoxy]piperidine (2.2 g) and anisole (5 ml) in

dichloromethane (10 ml) was added dropwise trifluoroacetic acid (10 ml) at 5°C with stirring. The mixture was stirred at room temperature for 3 hours and evaporated to dryness in vacuo at 70°C to give an oil (2.5 g). The mixture of the
5 above oil (2.5 g), 4-fluorobenzonitrile (1.5 g) and potassium carbonate (3 g) in dimethylsulfoxide (25 ml) was heated at 160°C for 3 hours with stirring. The reaction mixture was poured into ice-water and extracted with a mixture of ethyl acetate and tetrahydrofuran (1:1). The organic layer was
10 separated, washed with saturated sodium chloride aqueous solution and dried over magnesium sulfate. The magnesium sulfate was filtered by suction and the filtrate was concentrated under reduced pressure to give solid. The solid was subjected to column chromatography on silica gel (silica
15 gel 60 F₂₅₄, Merck) and eluted first a mixture of ethyl acetate and n-hexane (1:5), second a mixture of dichloromethane and methanol (10:1). The fractions containing the objective compound were combined and concentrated under reduced pressure to give 4-[4-(4-methoxybutoxy)piperidin-1-yl]benzonitrile (2.0 g).
20

NMR (CDCl₃, δ): 1.58-1.76 (6H, m), 1.89-2.00 (2H, m),
3.08-3.21 (2H, m), 3.33 (3H, s), 3.37-3.68 (7H, m),
6.85 (2H, d, J=9Hz), 7.46 (2H, d, J=9Hz)

MASS (m/z) (API-ES-Positive): 312 (M⁺+Na+1)

25

Preparation 27

The mixture of 4-[4-(4-methoxybutoxy)piperidin-1-yl]benzonitrile (2 g), thiosemicarbazide (1 g) and trifluoroacetic acid (10 ml) in toluene (20 ml) was stirred
30 at 60-65°C for 9 hours. The reaction mixture was poured into ice-water and adjusted to pH 9 using sodium hydroxide aqueous solution. The mixture was extracted with a mixture of ethyl acetate and tetrahydrofuran (1:1), washed with saturated sodium chloride aqueous solution and dried over magnesium
35 sulfate. The magnesium sulfate was filtered by suction, the

filtrate was concentrated under reduced pressure and the residue was triturated with isopropyl ether. The precipitates were collected by filtration, washed with isopropyl ether and dried in vacuo to give 2-amino-5-[4-(4-methoxybutoxy)piperidin-1-yl]phenyl][1,3,4]thiadiazole (2.0 g).

NMR (DMSO- d_6 , δ): 1.40-1.60 (6H, m), 1.80-2.00 (2H, m), 2.86-3.15 (2H, m), 3.23 (3H, s), 3.30-3.50 (5H, m), 3.50-3.61 (2H, m), 6.98 (2H, d, $J=8.9\text{Hz}$), 7.19 (2H, s), 7.54 (2H, d, $J=8.9\text{Hz}$)

MASS (m/z): 363 ($M^+ + 1$)

Preparation 28

A mixture of 2-amino-5-[4-(4-methoxybutoxy)piperidin-1-yl]phenyl[1,3,4]thiadiazole (2 g) and 4-(ethoxycarbonyl)phenacylbromide (2.3 g) in ethanol (25 ml) was refluxed for 6 hours with stirring. After cooling, the reaction mixture was poured into isopropyl ether. The precipitates were collected by filtration, washed with isopropyl ether and dried in vacuo to give solid. The mixture of this solid and trifluoroacetic acid (10 ml) in xylene (60 ml) was heated at 130°C for 6 hours with stirring. The reaction mixture was concentrated under reduced pressure and the residue was triturated with isopropyl ether. The precipitates were collected by filtration, washed with isopropyl ether and dried in vacuo to give ethyl-4-[2-[4-(4-methoxybutoxypiperidin-1-yl)phenyl]imidazo[2,1-b][1,3,4]-thiadiazol-6-yl]benzoate (2.4 g).

IR (KBr): 2939, 2854, 1708, 1604, 1469 cm^{-1}

NMR (DMSO- d_6 , δ): 1.34 (3H, t, $J=7.2\text{Hz}$), 1.40-1.65 (6H, m), 1.75-1.95 (4H, m), 3.00-3.20 (2H, m), 3.22 (3H, s), 3.25-3.40 (2H, m), 3.40-3.90 (3H, m), 4.33 (2H, q, $J=7.5\text{Hz}$), 7.02 (2H, d, $J=8.8\text{Hz}$), 7.57 (2H, d, $J=8.8\text{Hz}$), 7.75 (2H, d, $J=8.8\text{Hz}$), 8.00 (1H, s), 8.14 (2H, d, $J=9.0\text{Hz}$)

MASS (m/z): 535 ($M^+ + 1$)

Preparation 29

A solution of ethyl-4-[2-4-[4-methoxybutoxypiperidin-1-yl]phenyl]imidazo[2,1-b][1,3,4]thiadiazol-6-yl]benzoate (2.4 g) and 10% sodium hydroxide aqueous solution (15 ml) in methanol (50 ml) and tetrahydrofuran (25 ml) was refluxed for 6 hours with stirring. The reaction mixture was concentrated under reduced pressure, ice-water was added to the residue and adjusted to pH 3 using hydrochloric acid. The mixture was shaken with a mixture of ethyl acetate and tetrahydrofuran (1:1). The precipitates were collected by filtration, washed with water and dried in vacuo to give 4-[2-[4-(4-methoxybutoxy)piperidin-1-yl-phenyl]imidazo[2,1-b]-[1,3,4]thiadiazol-6-yl]benzoic acid (2 g).

IR (KBr): 2854, 2650, 2550, 1691, 1678, 1608, 1599, 1476 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ): 1.20-1.60 (6H, m), 1.60-2.05 (2H, m), 3.00-3.30 (2H, m), 3.22 (3H, m), 3.00-4.00 (7H, m), 7.10 (2H, d, $J=8.8\text{Hz}$), 7.75 (2H, d, $J=8.7\text{Hz}$), 7.99 (4H, m), 8.81 (1H, s), 12.90 (1H, br s)

MASS (m/z): 507 ($M^+ + 1$)

Preparation 30

To a solution of 4-[2-[4-(4-methoxybutoxypiperidin-1-yl)phenyl]imidazo[2,1-b][1,3,4]thiadiazol-6-yl]benzoic acid (2.4 g) in dichloromethane (150 ml) was added triethylamine (1.3 g), 3-(3-dimethylaminopropyl)-1-ethylcarbodiimide hydrochloride (2 g) and 1-hydroxybenzotriazole (1 g). The mixture was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure and the residue was triturated with water. The precipitates were collected by filtration, washed with water and isopropyl ether and dried in vacuo to give 4-[2-[4-(4-methoxybutoxy)piperidin-1-yl-phenyl]imidazo[2,1-

b][1,3,4]thiadiazol-6-yl]benzoic acid benzotriazol-1-yl ester
(2.5 g).

IR (KBr): 3427, 2937, 2856, 1774, 1602, 1471 cm^{-1}

5 NMR (DMSO-d_6 , δ): 1.30-1.65 (6H, m), 1.70-2.10 (2H, m),
3.21 (3H, m), 2.80-3.60 (7H, m), 3.60-3.80 (2H, m),
7.05-8.00 (10H, m), 8.00 (1H, s), 8.21 (1H, d,
J=8.6Hz), 8.33 (1H, d, J=8.6Hz)

MASS (m/z): 624 (M^+ +1)

10 The following compound was obtained according to a
similar manner to that of Preparation 26.

Preparation 31

4-(3-Methoxypropoxypiperidin-1-yl)benzonitrile

15 IR (KBr): 2931, 2866, 2215, 1678, 1604, 1516 cm^{-1}

NMR (DMSO-d_6 , δ): 1.35-1.60 (2H, m), 1.60-1.80 (2H, m),
1.80-2.00 (2H, m), 2.86-3.25 (2H, m), 3.21 (3H, s),
3.30-3.60 (5H, m), 3.60-3.80 (2H, m), 7.01 (2H, d,
J=9Hz), 7.55 (2H, d, J=8.9Hz)

20 MASS (m/z): 275 (M^+ +1)

The following compound was obtained according to a
similar manner to that of Preparation 27.

25 Preparation 32

2-Amino-5-[4-(3-methoxypropoxypiperidin-1-yl)phenyl]-
[1,3,4]thiadiazole

NMR (DMSO-d_6 , δ): 1.30-1.60 (2H, m), 1.65-1.80 (2H, m),
1.80-2.00 (2H, m), 2.80-3.20 (2H, m), 3.21 (3H, s),
30 3.30-3.70 (7H, m), 6.98 (2H, d, J=8.9Hz), 7.19 (2H,
br s), 7.54 (2H, d, J=8.8Hz)

MASS (m/z): 349 (M^+ +1)

The following compound was obtained according to a
35 similar manner to that of Preparation 28.

Preparation 33

Ethyl-4-[2-[4-(3-methoxypropoxypiperidin-1-yl)phenyl]imidazo[2,1-b][1,3,4]thiadiazol-6-yl]benzoate

- 5 IR (KBr): 3411, 3211, 3132, 2943, 2862, 1709, 1604 cm^{-1}
NMR (DMSO-d_6 , δ): 1.30-1.60 (5H, m), 1.65-1.80 (2H, m),
1.80-2.00 (2H, m), 2.80-3.10 (2H, m), 3.22 (3H, s),
3.30-3.80 (6H, m), 4.20-4.50 (3H, m), 6.98 (2H, d,
J=9Hz), 7.40 (1H, s), 7.54 (2H, d, J=8.8Hz), 7.80-
10 8.40 (4H, m)
MASS (m/z): 521 (M^+ +1)

The following compound was obtained according to a similar manner to that of Preparation 29.

Preparation 34

4-[2-[4-(3-Methoxypropoxypiperidin-1-yl)phenyl]-imidazo[2,1-b][1,3,4]thiadiazol-6-yl]benzoic acid

- 20 IR (KBr): 3423, 2935, 2858, 2650, 2550, 1682, 1603,
1468 cm^{-1}
NMR (DMSO-d_6 , δ): 1.40-1.60 (2H, m), 1.60-1.80 (2H, m),
1.80-2.00 (2H, m), 2.80-3.20 (2H, m), 3.22 (3H, s),
3.30-3.80 (7H, m), 6.98 (2H, d, J=8.7Hz), 7.19 (1H,
s), 7.54 (2H, d, J=8.7Hz), 7.80-8.20 (4H, m)
25 MASS (m/z): 493 (M^+ +1)

The following compound was obtained according to a similar manner to that of Preparation 30.

Preparation 35

4-[2-[4-(3-Methoxypropoxypiperidin-1-yl)phenyl]-imidazo[2,1-b][1,3,4]thiadiazol-6-yl]benzoic acid
benzotriazol-1-yl ester

- 35 IR (KBr): 3464, 3429, 3425, 3402, 2932, 2931, 1774,
1605, 1469 cm^{-1}

NMR (DMSO- d_6 , δ): 1.30-1.60 (2H, m), 1.60-1.80 (2H, m),
1.80-2.00 (2H, m), 2.80-3.30 (2H, m), 3.22 (3H, s),
3.35-3.80 (7H, m), 7.08 (2H, d, $J=9.1\text{Hz}$), 7.20-8.00
(8H, m), 8.00 (1H, s), 8.14 (1H, d, $J=8.6\text{Hz}$), 8.33
(1H, d, $J=8.5\text{Hz}$)

MASS (m/z): 610 (M^+ +1)

Preparation 36

A mixture of methyl 4-methylsulfinylbenzoate (6.0 g),
sodium acetate (11 g) and acetic anhydride (60 ml) was
stirred for 7.5 hours at 180°C. The reaction mixture was
cooled and filtered by suction. The filtrate was
concentrated under reduced pressure and the residue was
trituated with water. The precipitates were collected by
filtration, washed with aqueous sodium carbonate and water.
The solid was subjected to column chromatography on silica
gel (silica gel 60 F254, Merck: 200 g) and eluted with a
mixture of ethyl acetate and toluene (1:5). The fractions
containing the objective compound were combined and
concentrated under reduced pressure to give methyl 4-
acetoxymethylthiobenzoate (5.5 g).

IR (KBr): 1746, 1704, 1593 cm^{-1}

NMR (CDCl_3 , δ): 2.12 (3H, s), 3.92 (3H, s), 5.50 (2H,
s), 7.63 (2H, d, $J=8.3\text{Hz}$), 7.98 (2H, d, $J=8.3\text{Hz}$)

MASS (m/z) (API-ES-Positive): 263 (M^+ +23)

Preparation 37

To a solution of methyl 4-acetoxymethylthiobenzoate
(15.5 g) in a mixture of methanol (20 ml) and dichloromethane
(60 ml) was portionwise added magnesium monoperoxyphthalate
hexahydrate (24 g) at 5°C, with stirring. The mixture was
stirred at room temperature for 2 hours. The reaction
mixture was washed with ice-water, aqueous sodium carbonate
and brine, then dried over magnesium sulfate. The organic
solvent was concentrated under reduced pressure to give

acetoxyethyl-(4-methoxycarbonylphenyl)-
sulfone (5.9 g).

IR (KBr): 1759, 1724, 1434 cm^{-1}

NMR (CDCl_3 , δ): 2.09 (3H, s), 3.98 (3H, s), 5.18 (2H,
5 s), 8.01 (2H, d, $J=8.5\text{Hz}$), 8.26 (2H, d, $J=8.5\text{Hz}$)

MASS (m/z): 273 (M^++1)

Preparation 38

To a solution of methyl 4-acetoxyethylsulfon-
10 benzoate (5.5 g) in a mixture of tetrahydrofuran (50 ml) and
methanol (25 ml) was added dropwise 10% aqueous sodium
hydroxide at 5°C with stirring. The mixture was stirred at
room temperature for 3 hours. The reaction mixture was
concentrated under reduced pressure and to the residue was
15 added water. The solution was washed with toluene and the
aqueous layer was concentrated under reduced pressure and
dried in vacuo at 50°C to give sodium
methoxycarbonylbenzenesulfinate (4.5 g).

IR (KBr): 3424, 3300, 1718, 1594 cm^{-1}

20 NMR ($\text{DMSO}-d_6$, δ): 3.84 (3H, s), 7.60 (2H, d, $J=8.0\text{Hz}$),
7.92 (2H, d, $J=8.0\text{Hz}$)

MASS (m/z) (API-ES-Positive): 245 (M^++23)

Preparation 39

25 A mixture of sodium-4-(1-methoxycarbonyl)benzene
sulfinate (2.2 g) and 1,7-dibromoheptane (2.6 g) in N,N-
dimethylformamide (50 ml) was stirred at 100°C for 5 hours.
The reaction mixture was concentrated under reduced pressure
and the residue was triturated with water. The mixture was
30 extracted with a mixture of ethyl acetate and tetrahydrofuran
(1:1), washed with brine and dried over magnesium sulfate.
After removing the magnesium sulfate, the filtrate was
concentrated under reduced pressure to give a yellow oil. The
oily product was subjected to column chromatography on silica
35 gel (silica gel 60 F254, Merck: 250 g) and eluted with a

mixture of ethyl acetate and toluene (1:10). The fractions containing the objective compound were combined and concentrated under reduced pressure to give 7-bromoheptyl-[4-(methoxycarbonyl)phenyl]sulfone (1.4 g).

- 5 IR (Neat): 3423, 2927, 2852, 1725, 1280 cm^{-1}
NMR (CDCl_3 , δ): 1.20-1.43 (6H, m), 1.60-1.85 (4H, m),
3.11 (2H, m), 3.38 (2H, t, $J=6.7\text{Hz}$), 3.98 (3H, s),
8.00 (2H, d, $J=8.4\text{Hz}$), 8.23 (2H, d, $J=8.4\text{Hz}$)
MASS (m/z): 379 (M^+)

10

Preparation 40

- A mixture of 7-bromoheptyl-[(4-methoxycarbonyl)-phenyl]sulfone (1.4 g) and sodium methoxide in methanol solution (28%) (2 ml) in methanol (20ml) was refluxed for 10
15 hours with stirring. The reaction mixture was concentrated under reduced pressure and subjected to column chromatography on silica gel (silica gel 60 F254, Merck) and eluted with a mixture of ethyl acetate and toluene (1:5-1:3). The fractions containing the objective compound were combined and
20 concentrated under reduced pressure to give 7-methoxyheptyl-[4-(methoxycarbonyl)phenyl]sulfone (0.85 g).

- IR (Neat): 2929, 2857, 1723, 1280 cm^{-1}
NMR (CDCl_3 , δ): 3.15-3.40 (8H, m), 3.40-3.80 (4H, m),
3.98 (3H, s), 8.00 (2H, d, $J=8.5\text{Hz}$), 8.23 (2H, d,
25 $J=8.5\text{Hz}$)
MASS (m/z): 328 ($M^+ + 1$)

Preparation 41

- A mixture of 7-methoxyheptyl-[4-(methoxycarbonyl)-phenyl]sulfone (0.85 g) and 1N-aqueous sodium hydroxide (5
30 ml) in a mixture of ethanol (20 ml) and tetrahydrofuran (10 ml) was stirred at 80°C for 5 hours. The reaction mixture was concentrated under reduced pressure and the residue was triturated with water. The solution was adjusted to pH 1.0
35 using diluted hydrochloric acid. The precipitates were

collected by filtration, washed with water and dried in vacuo to give 7-methoxyheptyl-(4-carboxyphenyl)sulfone (0.8 g) white solid.

IR (KBr): 2674, 2555, 1698, 1425, 1285 cm^{-1}

5 NMR (DMSO- d_6 , δ): 1.1-1.4 (6H, m), 1.40-1.60 (4H, m),
3.21 (3H, s), 3.18-3.40 (4H, m), 8.00 (2H, d,
J=8.5Hz), 8.18 (2H, d, J=8.5Hz)

MASS (m/z): 315 ($M^+ + 1$)

10 Preparation 42

A mixture of 7-methoxyheptyl-4-carboxyphenyl-sulfone (0.8 g) and thionyl chloride (10 ml) was refluxed for 2 hours with stirring. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in
15 tetrahydrofuran (10 ml). To a mixture of 4-(methoxycarbonyl)benzamide oxime (0.49 g) in pyridine (25 ml) was added dropwise the above acid chloride solution at 5°C with stirring. The mixture was stirred at 5°C for 0.5 hour and continued at room temperature for an hour. The reaction
20 mixture was concentrated under reduced pressure and the residue was triturated with water. The precipitates were collected by filtration, washed with water and dried to give 4-(methoxycarbonyl)-O-4'-[(7-methoxyheptylsulfonyl)-benzoyl]benzamide oxime (1.0 g).

25 IR (KBr): 3492, 3369, 2933, 2857, 1724, 1616, 1276 cm^{-1}

NMR (DMSO- d_6 , δ): 1.15-1.54 (12H, m), 3.23 (3H, s),
3.22-3.40 (2H, m), 3.90 (3H, s), 7.25 (2H, br s),
7.95 (2H, d, J=8.3Hz), 8.00-8.17 (4H, m), 8.47 (2H, d, J=8.3Hz)

30 MASS (m/z): 491 ($M^+ + 1$)

Preparation 43

A solution of 4-methoxycarbonyl-O-[4'-(7-methoxyheptylsulfonyl)benzoyl]benzamide oxime (1.0 g) in N,N-dimethylformamide (10 ml) was stirred at 100°C for 6 hours.

The reaction mixture was poured into ice-water and adjusted to pH 1 using diluted hydrochloric acid. The precipitates were collected by filtration, washed with water and dried to give methyl-4-[5-[4-(7-methoxyheptyl-

5 sulfonyl)phenyl]-1,2,4-oxadiazol-3-yl]benzoate (0.82 g).

IR (KBr): 2931, 2857, 1724, 1280 cm^{-1}

NMR (DMSO- d_6 , δ): 1.20-1.60 (10H, m), 3.17 (3H, s),
3.22-3.43 (4H, m), 3.92 (3H, s), 8.17-8.30 (6H, m),
8.47 (2H, d, $J=8.3\text{Hz}$)

10 MASS (m/z): 473 (M^++1)

Preparation 44

A mixture of methyl 4-[5-[4-(7-methoxyheptylsulfonyl)phenyl]-1,2,4-oxazol-3-yl]benzoate (0.8
15 g) and 10% sodium hydroxide aqueous solution (2 ml) in a mixture of ethanol (25 ml) and tetrahydrofuran (10 ml) was refluxed for 3.5 hours with stirring. The reaction mixture was concentrated under reduced pressure and to the residue was added water and adjusted to pH 1 using diluted
20 hydrochloric acid. The precipitates were collected by filtration, washed with water and dried to give 4-[5-[4-(7-methoxyheptylsulfonyl)phenyl]-1,2,4-oxadiazol-3-yl]benzoic acid (0.8 g).

IR (KBr): 2931, 2857, 2750, 2650, 1693, 1415 cm^{-1}

25 NMR (DMSO- d_6 , δ): 1.15-1.60 (10H, m), 3.18 (3H, s),
3.20-3.50 (4H, m), 8.16-8.30 (6H, m), 8.47 (2H, d,
 $J=8.4\text{Hz}$)

MASS (m/z): 459 (M^++1)

Preparation 45

To a solution of 4-[5-[4-(7-methoxyheptylsulfonyl)-phenyl]-1,2,4-oxazol-3-yl]benzoic acid (0.8 g) and triethylamine (0.4 g) in dichloromethane (30 ml) was added 3-(3-dimethylaminopropyl)-1-ethylcarbodiimide (0.7 g) and 1-
35 hydroxybenzotriazole (0.36 g). The mixture was stirred at

room temperature for 8 hours. The reaction mixture was washed with water, saturated sodium chloride aqueous solution and dried over magnesium sulfate. After magnesium sulfate was filtered off, the filtrate was concentrated under reduced pressure and the residue was triturated with isopropyl ether.

The precipitates were collected by filtration, washed with isopropyl ether and dried in vacuo to give 4-[5-{4-(7-methoxyheptylsulfonyl)phenyl}-1,2,4-oxadiazol-3-yl]benzoic acid benzotriazol-1-yl ester (0.89 g).

- 10 IR (KBr): 2931, 2857, 1787, 1616, 1409, 1282 cm^{-1}
NMR (DMSO-d_6 , δ): 1.10-1.50 (10H, m), 3.18 (3H, s),
3.22-3.40 (4H, m), 7.25-7.60 (2H, m), 7.70 (1H, d, $J=8.5\text{Hz}$), 7.96 (1H, d, $J=8.5\text{Hz}$), 8.19-8.24 (6H, m),
8.47 (2H, d, $J=8.3\text{Hz}$)
15 MASS (m/z): 576 ($M^+ + 1$)

The following compound was obtained according to a similar manner to that of Preparation 39.

20 Preparation 46

1-[4-(Methoxycarbonyl)phenylsulfonyl]-9-bromoheptane

IR (KBr): 2925, 2850, 1724, 1461, 1280 cm^{-1}

- NMR (DMSO-d_6 , δ): 1.10-1.35 (10H, m), 1.40-1.55 (2H, m),
1.60-1.80 (2H, m), 3.33-3.41 (2H, m), 3.50 (2H, t, $J=6.7\text{Hz}$), 3.91 (3H, s), 8.05 (2H, d, $J=8.4\text{Hz}$), 8.20
25 (2H, d, $J=8.4\text{Hz}$)
MASS (m/z): 405 (M^+)

- The following compound was obtained according to a similar manner to that of Preparation 40.

Preparation 47

1-[4-(Methoxycarbonyl)phenylsulfonyl]-9-methoxyheptane

IR (KBr): 2927, 2854, 1699, 1425, 1286 cm^{-1}

- NMR (DMSO-d_6 , δ): 1.10-1.30 (10H, m), 1.30-1.48 (6H, m),
35

3.19 (3H, s), 3.23-3.39 (4H, m), 3.90 (3H, s), 8.01 (2H, d, J=8.3Hz), 8.17 (2H, d, J=8.3Hz)

MASS (m/z): 357 ($M^+ + 1$)

- 5 The following compound was obtained according to a similar manner to that of Preparation 41.

Preparation 48

1-[4-Carboxyphenylsulfonyl]-9-methoxyheptane

- 10 IR (KBr): 2937, 2852, 2672, 2550, 1698, 1425, 1320, 1286 cm^{-1}

NMR (DMSO-d_6 , δ): 1.10-1.30 (10H, m), 1.40-1.47 (4H, m), 3.19 (3H, s), 3.23-3.39 (3H, m), 8.01 (2H, d, J=8.3Hz), 8.17 (2H, d, J=8.3Hz)

- 15 MASS (m/z): 343 ($M^+ + 1$)

The following compound was obtained according to a similar manner to that of Preparations 42 and 43.

- 20 Preparation 49

Methyl 4-[5-[4-(9-methoxy-n-nonylsulfonyl)phenyl]-1,2,4-oxadiazol-3-yl]benzoate

IR (KBr): 2925, 2854, 1724, 1612, 1409, 1278 cm^{-1}

- 25 NMR (DMSO-d_6 , δ): 1.19-1.57 (14H, m), 3.17 (3H, s), 3.12-3.43 (4H, m), 3.92 (3H, s), 8.17-8.30 (6H, m), 8.47 (2H, d, J=8.4Hz)

MASS (m/z): 501 ($M^+ + 1$)

- 30 The following compound was obtained according to a similar manner to that of Preparation 44.

Preparation 50

4-[5-[4'-(9-Methoxy-n-nonylsulfonyl)phenyl]-1,2,4-oxadiazol-3-yl]benzoic acid

- 35 IR (KBr): 2927, 2854, 2667, 2550, 1691, 1614, 1415,

1282 cm^{-1}

NMR (DMSO-d_6 , δ): 1.10-1.30 (10H, m), 1.30-1.60 (4H, m),
3.17 (3H, s), 3.19-3.46 (4H, m), 8.00-8.27 (6H, m),
8.47 (2H, d, $J=8.3\text{Hz}$), 13.34 (1H, br s)

5 MASS (m/z): 487 (M^++1)

The following compound was obtained according to a similar manner to that of Preparation 45.

10 Preparation 51

4-[5-[4-(9-Methoxy-n-nonylsulfonyl)phenyl]-1,2,4-oxadiazol-3-yl]benzoic acid benzotriazol-1-yl ester

IR (KBr): 2927, 2854, 1785, 1614, 1411, 1282 cm^{-1}

15 NMR (DMSO-d_6 , δ): 1.10-1.30 (10H, m), 1.30-1.60 (4H, m),
3.17 (3H, s), 3.03-3.43 (4H, m), 7.36-7.58 (2H, m),
7.72 (1H, d, $J=8.3\text{Hz}$), 7.98 (1H, d, $J=8.3\text{Hz}$), 8.17-
8.27 (6H, m), 8.47 (2H, d, $J=8.4\text{Hz}$)

MASS (m/z): 604 (M^++1)

20 Preparation 52

To a mixture of methyl 4-hydroxybenzoate (1.52 g) and potassium carbonate (0.76 g) in acetone (30 ml) was added dropwise a solution of 1,7-dibromoheptane (3.1 g) in acetone (10 ml) at room temperature with stirring. The mixture was
25 stirred at room temperature for 2.5 hours, and then refluxed for overnight with stirring. The reaction mixture was filtered under reduced pressure and the filtrate was concentrated under reduced pressure to give an oily solid. The oily solid was subjected to column chromatography on
30 silica gel (silica gel 60 F254, Merck: 200 g) and eluted with a mixture of ethyl acetate and n-hexane (1:3). The fractions containing the objective compound were combined and concentrated under reduced pressure to give methyl 4-(7-bromo-n-heptyloxy)benzoate (2.3 g).

35 NMR (CDCl_3 , δ): 1.43-1.60 (6H, m), 1.74-1.90 (4H, m),

3.42 (2H, t, J=6.8Hz), 3.88 (3H, s), 4.00 (2H, t, J=6.8Hz), 6.89 (2H, d, J=8.9Hz), 7.98 (2H, d, J=8.9Hz)

MASS (m/z) (API-ES-Positive): 329 (M^+)

5

Preparation 53

A solution of methyl 4-[7-bromo-n-heptyloxy]benzoate (2.3 g) in methanol (50 ml) and a solution of 28% sodium methoxide in methanol (3.5 ml) was refluxed for 12 hours with stirring. The reaction mixture was concentrated under reduced pressure and water was added to the residue and adjusted to pH 1 using hydrochloric acid. The precipitates were collected by filtration, washed with water and dried in vacuo to give an oil. The oil was subjected to column chromatography on silica gel (silica gel 60 F254, Merck: 100 g) and eluted with a mixture of ethyl acetate and n-hexane (1:5). The fractions containing the objective compound were combined and concentrated under reduced pressure to give methyl 4-(7-methoxyheptyloxy)benzoate (1.6 g) as an oil.

15

IR (Neat): 2937, 2867, 1718, 1607, 1469, 1442 cm^{-1}

NMR (CDCl_3 , δ): 1.15-1.60 (8H, m), 1.60-1.84 (2H, m), 3.33 (3H, s), 3.30-3.40 (2H, t, J=6.4Hz), 3.88 (3H, s), 4.00 (2H, t, J=6.4Hz), 6.92 (2H, d, J=8.8Hz), 8.00 (2H, d, J=8.8Hz)

20

MASS (m/z): 281 ($M^+ + 1$)

Preparation 54

A mixture of methyl 4-(7-methoxy-n-heptyloxy)benzoate (1.5 g) and 1N-sodium hydroxide aqueous solution in ethanol (10 ml) and tetrahydrofuran (10 ml) was heated at 40-60°C for 5 hours with stirring. The reaction mixture was concentrated under reduced pressure and water added to the residue and adjusted to pH 1 using hydrochloric acid. The precipitates were collected by filtration, washed with water and dried in vacuo to give 4-[7-methoxy-n-heptyloxy]benzoic acid (1.4 g)

35

as a white solid.

IR (KBr): 2937, 2857, 2665, 2561, 1691, 1666, 1606,
1428 cm^{-1}

5 NMR ($\text{DMSO}-d_6$, δ): 1.20-1.55 (8H, m), 1.60-1.80 (2H, m),
3.20 (3H, s), 3.29 (2H, d, $J=6.4\text{Hz}$), 4.03 (2H, d,
 $J=6.4\text{Hz}$), 7.00 (2H, d, $J=8.7\text{Hz}$), 7.87 (2H, d,
 $J=8.7\text{Hz}$)

MASS (m/z)(API-ES-Positive): 289 (M^++23), 249

10 Preparation 55

A mixture of 4-(7-methoxy-n-heptyloxy)benzoic acid (4 g)
and thionyl chloride (40 ml) was refluxed for 2 hours with
stirring. The reaction mixture was concentrated under
reduced pressure and the residue was dissolved in
15 tetrahydrofuran (40 ml). To a mixture of 4-
(methoxycarbonyl)benzamide oxime (2.8 g) in pyridine (30 ml)
was added dropwise the above acid chloride solution at 5°C
with stirring. The mixture was stirred at 5°C for 0.5 hour
and continued at room temperature for 0.5 hour. The reaction
20 mixture was poured into water. The precipitates were
collected by filtration, washed with water and dried in vacuo
to give 4-(methoxycarbonyl)-O-[4-(7-methoxy-n-
heptyloxy)benzoyl]benzamide oxime (6.0 g).

IR (KBr): 3478, 3372, 2931, 2854, 1714, 1605 cm^{-1}

25 NMR ($\text{DMSO}-d_6$, δ): 1.20-1.55 (8H, m), 1.60-1.80 (2H, m),
3.21 (3H, s), 3.30 (3H, t, $J=6.4\text{Hz}$), 3.89 (3H, s),
4.07 (2H, t, $J=6.4\text{Hz}$), 7.03 (2H, d, $J=8.4\text{Hz}$), 7.08
(2H, br s), 7.92 (2H, d, $J=8.4\text{Hz}$), 8.05 (2H, d,
 $J=8.4\text{Hz}$), 8.14 (2H, d, $J=8.8\text{Hz}$)

30 MASS (m/z): 443 (M^++1)

Preparation 56

A solution of 4-(methoxycarbonyl)-O-[4-(7-methoxy-n-
heptyloxy)benzoyl]benzamide oxime (6.0 g) in N,N-
35 dimethylformamide (60 ml) was stirred at 100°C for 24 hours.

The reaction mixture was concentrated under reduced pressure and water added to the residue and adjusted to pH 1 using hydrochloric acid. The precipitates were collected by filtration, washed with water and dried in vacuo to give a solid. The solid was subjected to column chromatography on silica gel (silica gel 60 F254, Merck: 300 g) and eluted with a mixture of ethyl acetate and toluene (1:10-1:5). The fractions containing the objective compound were combined and concentrated under reduced pressure to give methyl 4-[5-[4-(7-methoxy-n-heptyloxy)phenyl]-1,2,4-oxadiazol-3-yl]benzoate (5.4 g).

IR (KBr): 2939, 2863, 1722, 1612, 1471, 1417, 1270 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ): 1.15-1.60 (8H, m), 1.60-1.80 (2H, m), 2.10-2.20 (2H, m), 3.21 (3H, s), 3.90 (3H, s), 4.10 (2H, t, $J=6.3\text{Hz}$), 7.20 (2H, d, $J=8.5\text{Hz}$), 8.12-8.27 (6H, m)

MASS (m/z): 425 (M^++1)

Preparation 57

A mixture of methyl 4-[5-4-(7-methoxy-n-heptyloxy)phenyl]-1,2,4-oxadiazol-3-yl]benzoate (5.4 g) and 10% sodium hydroxide aqueous solution (15 ml) in ethanol (60 ml) and tetrahydrofuran (30 ml) was stirred at 60-70°C for 2 hours. The reaction mixture was concentrated under reduced pressure and water added to the residue and adjusted to pH 1 using hydrochloric acid. The precipitates were collected by filtration, washed with water and dried in vacuo to give 4-[5-[4-(7-methoxy-n-heptyloxy)phenyl]-1,2,4-oxadiazol-3-yl]benzoic acid (4.4 g).

IR (KBr): 2931, 2857, 2667, 2560, 1693, 1614, 1419 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ): 1.10-1.50 (8H, m), 1.60-1.80 (2H, m), 3.21 (3H, s), 4.10 (2H, t, $J=6.3\text{Hz}$), 7.18 (2H, d, $J=9.1\text{Hz}$), 7.90-8.10 (4H, m), 8.13 (2H, d, $J=8.9\text{Hz}$)

MASS (m/z): 411 (M^++1)

Preparation 58

To a mixture of 4-[5-[4-(7-methoxy-n-heptyloxy)-phenyl]-1,2,4-oxadiazol-3-yl]benzoic acid (2.0 g) and triethylamine (1.1 g) in dichloromethane (60 ml) was added 3-(3-dimethylaminopropyl)-1-ethylcarbodiimide hydrochloride (1.4 g) and 1-hydroxybenzotriazole (0.8 g). The mixture was stirred at room temperature overnight. The reaction mixture was washed with water, brine and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was concentrated under reduced pressure, and the residue was triturated with isopropyl ether. The precipitates were collected by filtration, washed with isopropyl ether and dried to give 4-[5-[4-(7-methoxy-n-heptyloxy)phenyl]-1,2,4-oxadiazol-3-yl]benzoic acid benzotriazol-1-yl ester (2.1 g).

IR (KBr): 2933, 2859, 1781, 1612 cm^{-1}

NMR (CDCl_3 , δ): 1.30-1.70 (8H, m), 1.65-1.90 (2H, m), 3.24 (3H, s), 3.39 (2H, t, $J=6.4\text{Hz}$), 4.06 (2H, t, $J=6.4\text{Hz}$), 7.05 (2H, d, $J=8.9\text{Hz}$), 7.40-7.65 (3H, m), 8.10-8.25 (3H, m), 8.42 (4H, s)

MASS (m/z): 528 ($M^+ + 1$)

The following compound was obtained according to a similar manner to that of Preparation 52.

Preparation 59

Methyl 4-(9-bromo-n-nonyloxy)benzoate

IR (KBr): 2940, 2923, 2856, 1711, 1604, 1511 cm^{-1}

NMR (CDCl_3 , δ): 1.20-1.50 (10H, m), 1.60-1.90 (4H, m), 3.41 (2H, t, $J=6.8\text{Hz}$), 3.88 (3H, s), 4.00 (2H, t, $J=6.8\text{Hz}$), 6.91 (2H, d, $J=8.8\text{Hz}$), 7.98 (2H, d, $J=8.7\text{Hz}$)

MASS (m/z): 357 (M^+)

The following compound was obtained according to a

similar manner to that of Preparation 53.

Preparation 60

Methyl 4-(9-methoxy-n-nonyloxy)benzoate

- 5 IR (KBr): 2929, 2852, 1724, 1606 cm^{-1}
NMR (CDCl_3 , δ): 1.20-1.40 (10H, m), 1.45-1.60 (2H, m),
1.65-1.83 (2H, m), 3.33 (3H, s), 3.37 (2H, t,
J=6.5Hz), 3.88 (3H, s), 4.01 (2H, t, J=6.5Hz), 6.90
(2H, d, J=8.9Hz), 8.00 (2H, d, J=8.9Hz)
10 MASS (m/z): 308 (M^+ +1)

The following compound was obtained according to a similar manner to that of Preparation 54.

15 Preparation 61

4-(9-Methoxy-n-nonyloxy)benzoic acid

- IR (KBr): 2929, 2856, 2650, 2560, 1695, 1664, 1610 cm^{-1}
NMR ($\text{DMSO}-d_6$, δ): 1.20-1.35 (10H, m), 1.40-1.60 (2H, m),
1.60-1.80 (2H, m), 3.20 (3H, s), 3.28 (2H, t,
20 J=6.4Hz), 4.02 (2H, t, J=6.4Hz), 7.00 (2H, d,
J=8.7Hz), 7.87 (2H, d, J=8.7Hz)

The following compound was obtained according to a similar manner to that of Preparation 55.

25

Preparation 62

4-(Methoxycarbonyl)-O-4'-(9-methoxy-n-nonyloxy)benzoyl-benzamide oxime

- IR (KBr): 3488, 3367, 2929, 2856, 1719, 1615, 1589 cm^{-1}
30 NMR ($\text{DMSO}-d_6$, δ): 1.20-1.40 (10H, m), 1.40-1.60 (2H, m),
1.60-1.80 (2H, m), 3.20 (3H, s), 3.28 (2H, t,
J=6.5Hz), 3.89 (3H, s), 4.00 (2H, t, J=6.4Hz), 7.03
(2H, d, J=8.9Hz), 7.07 (2H, br s), 7.92 (2H, d,
J=8.4Hz), 8.05 (2H, d, J=8.4Hz), 8.14 (2H, d,
35 J=8.9Hz)

MASS (m/z): 471 ($M^+ + 1$)

The following compound was obtained according to a similar manner to that of Preparation 56.

5

Preparation 63

Methyl 4-[5-[4-(9-methoxy-n-nonyloxy)phenyl]-1,2,4-oxadiazol-3-yl]benzoate

IR (KBr): 2933, 2856, 1722, 1616, 1276 cm^{-1}

10 NMR (DMSO- d_6 , δ): 1.20-1.40 (10H, m), 1.40-1.60 (2H, m),
1.60-1.80 (2H, m), 3.27-3.33 (2H, m), 3.20 (3H, s),
4.00 (3H, s), 4.05-4.11 (2H, m), 7.19 (2H, d,
J=9Hz), 7.90 (2H, d, J=9Hz), 8.12-8.25 (4H, m)

MASS (m/z): 453 ($M^+ + 1$)

15

The following compound was obtained according to a similar manner to that of Preparation 57.

Preparation 64

20 4-[5-[4-(9-Methoxy-n-nonyloxy)phenyl]-1,2,4-oxadiazol-3-yl]benzoic acid

IR (KBr): 2931, 2857, 2667, 2560, 1693, 1614, 1419 cm^{-1}

NMR (DMSO- d_6 , δ): 1.15-1.40 (10H, m), 1.40-1.50 (2H, m),
1.60-1.80 (2H, m), 3.21 (3H, s), 3.27 (2H, t,
25 J=6.5Hz), 4.10 (2H, t, J=6.5Hz), 7.18 (2H, d,
J=8.8Hz), 8.10-8.25 (6H, m)

MASS (m/z): 439 ($M^+ + 1$)

30 The following compound was obtained according to a similar manner to that of Preparation 58.

Preparation 65

4-[5-[4-(9-Methoxy-n-nonyloxy)phenyl]-1,2,4-oxadiazol-3-yl]benzoic acid benzotriazol-1-yl ester

35 IR (KBr): 2931, 2856, 1781, 1612 cm^{-1}

NMR (CDCl₃, δ): 1.20-1.40 (10H, m), 1.40-1.60 (2H, m),
1.60-1.80 (2H, m), 3.33 (3H, s), 3.37 (2H, t,
J=6.5Hz), 4.06 (2H, t, J=6.5Hz), 7.05 (2H, d,
J=8.8Hz), 7.40-7.60 (3H, m), 8.10-8.20 (3H, m),
5 8.42 (4H, br s)
MASS (m/z): 556 (M⁺+1)

Preparation 66

A mixture of 4-bromophenol (10 g), 1,6-dibromohexane
10 (49.4 g) and potassium carbonate (9.59 g) in N,N-
dimethylformamide (50 ml) was stirred for 4 hours at 60°C
(bath temp.), and then cooled to ambient temperature. To the
reaction mixture was added ethyl acetate (200 ml), and the
mixture was washed with water (200 ml x 2) and brine. The
15 organic layer was dried over magnesium sulfate. Magnesium
sulfate was filtered off, and the filtrate was evaporated
under reduced pressure to give a crude product. The crude
product was purified by silica gel chromatography (1:0-1:1
hexane-ethyl acetate) to give 1-bromo-4-(6-bromohexyloxy)-
20 benzene (15.61 g)

IR (KBr): 2940.9, 2910.1, 2861.8, 1490.7, 1467.6,
1292.1, 1245.8 cm⁻¹

NMR (DMSO-d₆, δ): 1.3-1.5 (4H, m), 1.6-2.0 (4H, m), 3.54
(2H, t, J=6.6Hz), 3.94 (2H, t, J=6.4Hz), 6.90 (2H,
25 d, J=4.5Hz), 7.43 (2H, d, J=4.5Hz)

Preparation 67

A mixture of 1-bromo-4-(6-bromohexyloxy)benzene (6.0 g)
and sodium methylate (28% in methanol) (10.3 ml) in methanol
30 (30 ml) was stirred for 2 hours at 70°C (bath temp.), and
then the solvent was evaporated. The residue was neutralized
by 1N-hydrochloric acid and extracted with ethyl acetate (100
ml), and washed with water and brine. The organic layer was
dried over magnesium sulfate. Magnesium sulfate was filtered
35 off, and the filtrate was evaporated under reduced pressure

to give a crude product. The crude product was purified by silica gel chromatography (20:1-10:1 hexane-ethyl acetate) to give 1-bromo-4-(6-methoxyhexyloxy)benzene (15.61 g) as a colorless oil.

5 IR (KBr): 2937.1, 2861.8, 1591.0, 1488.8, 1473.3,
1286.3, 1243.9, 823.5 cm^{-1}

NMR (DMSO-d_6 , δ): 1.2-1.6 (6H, m), 1.6-1.8 (2H, m), 3.21
(3H, s), 3.30 (2H, t, $J=6.4\text{Hz}$), 3.93 (2H, t,
 $J=6.4\text{Hz}$), 6.90 (2H, d, $J=6.8\text{Hz}$), 7.42 (2H, d,
10 $J=6.8\text{Hz}$)

Preparation 68

Under a nitrogen atmosphere, to a mixture of 1-bromo-4-(6-methoxyhexyloxy)benzene (3.68 g), 2-methyl-3-butyn-2-ol
15 (1.86 ml) and triethylamine (18 ml) in pyridine (7.4 ml) was added triphenylphosphine (67.2 mg), copper(I) iodide (24.4 mg) and dichlorobis(triphenylphosphine)palladium(II) (18.0 mg), and refluxed overnight. After cooling, insoluble material was filtered off and washed with isopropyl ether.
20 The filtrate was evaporated under reduced pressure. To the residue was added isopropyl ether and the mixture was washed with 0.1N-hydrochloric acid, water and brine. The organic layer was dried over magnesium sulfate. Magnesium sulfate was filtered off, and the filtrate was evaporated under
25 reduced pressure to give a crude yellow oil. The crude yellow oil was purified by silica gel chromatography (10:1-2:1 hexane-ethyl acetate) to give 4-[4-(6-methoxyhexyloxy)-phenyl]-2-methyl-3-butyn-2-ol (3.17 g) as a yellow powder.

IR (KBr): 3426.9, 3415.3, 2979.5, 2937.1, 2858.0,
30 2219.7, 1606.4, 1510.0, 1243.9, 1168.7,
1105.0 cm^{-1}

NMR (DMSO-d_6 , δ): 1.2-1.6 (12H, m), 1.6-1.8 (2H, m),
3.20 (3H, s), 3.30 (2H, t, $J=6.4\text{Hz}$), 3.95 (2H, t,
 $J=6.4\text{Hz}$), 5.39 (1H, s), 6.89 (2H, d, $J=8.7\text{Hz}$), 7.29
35 (2H, d, $J=8.7\text{Hz}$)

Preparation 69

- Under a nitrogen atmosphere, to a solution of 4-[4-(6-methoxyhexyloxy)phenyl]-2-methyl-3-butyne-2-ol (3.0 g) in
5 toluene (18 ml) was added sodium hydride (abt. 60% in oil suspension), and the mixture was refluxed for 2 hours. After cooling, to the reaction mixture was added isopropyl ether (100 ml) and water (100 ml), and neutralized by 1N-hydrochloric acid. The organic layer was separated, washed
10 with water and brine, dried over magnesium sulfate. Magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure to give a crude red oil. The crude red oil was purified by silica gel chromatography (10:1 hexane-ethyl acetate) to give 1-ethynyl-4-(6-methoxyhexyloxy)benzene (2.39 g) as an orange powder.
15 IR (KBr): 3263.0, 2929.3, 2861.8, 2100.1, 1604.5, 1510.0, 1249.6, 1116.6, 840.8 cm^{-1}
NMR (DMSO- d_6 , δ): 1.2-1.6 (6H, m), 1.6-1.8 (2H, m), 3.21 (3H, s), 3.30 (2H, t, $J=6.4\text{Hz}$), 3.97 (2H, t, $J=6.4\text{Hz}$), 4.00 (1H, s), 6.91 (2H, d, $J=8.7\text{Hz}$), 7.39 (2H, d, $J=8.7\text{Hz}$)
20 MASS (m/z): 233.3 (M^++1)

Preparation 70

- 25 To a solution of 4-methoxycarbonylphenylhydroxyimino-methyl chloride (975 mg) and 1-ethynyl-4-(6-methoxyhexyloxy)benzene (1.06 g) in tetrahydrofuran (10 ml) was added triethylamine (0.83 ml) in tetrahydrofuran (10 ml) over a period of 30 minutes at 40°C, and the mixture was
30 stirred at 40°C for 3 hours and 30 minutes. The mixture was diluted with dichloromethane and washed with water and brine. The separated organic layer was dried over magnesium sulfate and evaporated under reduced pressure. The residue was triturated with acetonitrile. The precipitate was collected
35 by filtration and dried to give 4-[5-[4-(6-

methoxyhexyloxy)phenyl]isoxazol-3-yl]benzoic acid methyl ester (1.37 g).

IR (KBr): 2937.1, 2859.9, 1716.3, 1278.6, 1116.6 cm^{-1}

NMR (CDCl_3 , δ): 1.3-1.7 (6H, m), 1.7-2.0 (2H, m), 3.34 (3H, s), 3.39 (2H, t, $J=6.3\text{Hz}$), 3.95 (3H, s), 4.02 (2H, t, $J=6.4\text{Hz}$), 4.00 (1H, s), 6.74 (1H, s), 6.98 (2H, d, $J=8.8\text{Hz}$), 7.77 (2H, d, $J=8.8\text{Hz}$), 7.94 (2H, d, $J=8.4\text{Hz}$), 8.14 (2H, d, $J=8.4\text{Hz}$)

MASS (m/z): 410 ($M^+ + 1$)

Preparation 71

To a solution of 4-[5-[4-(6-methoxyhexyloxy)phenyl]-isoxazol-3-yl]benzoic acid methyl ester (1.0 g) in a mixture of ethanol (10 ml) and tetrahydrofuran (20 ml) was added 10% sodium hydroxide aqueous solution (4.4 ml) and refluxed for 1 hour. The reaction mixture was adjusted to pH 1-2 with 1N-hydrochloric acid, and the resulting precipitate was collected by filtration to give 4-[5-[4-(6-methoxyhexyloxy)phenyl]isoxazol-3-yl]benzoic acid (964.2 mg).

IR (KBr): 2939.0, 2863.8, 2669.0, 2545.6, 1685.5, 1616.1, 1284.4, 1253.5 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ): 1.2-1.6 (6H, m), 1.6-1.9 (2H, m), 3.21 (3H, s), 3.31 (2H, t, $J=6.2\text{Hz}$), 4.04 (2H, t, $J=6.4\text{Hz}$), 6.11 (2H, d, $J=8.8\text{Hz}$), 7.54 (1H, s), 7.85 (2H, d, $J=8.7\text{Hz}$), 8.07 (2H, d, $J=8.4\text{Hz}$), 8.15 (2H, d, $J=8.4\text{Hz}$)

MASS (m/z): 396 ($M^+ + 1$)

Preparation 72

A mixture of 1-bromo-4-fluorobenzene (10 g), cis-2,6-dimethylmorpholine (7.74 ml) and potassium carbonate (15.8 g) in dimethylsulfoxide (50 ml) was stirred for 25 hours at 150°C. The reaction mixture was cooled and poured into water (500 ml), and stirred for 10 minutes. The reaction mixture was extracted with ethyl acetate (100 ml x 2), washed with

brine, dried over magnesium sulfate and evaporated under reduced pressure to give a crude yellow oil (680 mg). The crude oil was purified by silica gel chromatography (1:0-10:1 hexane-ethyl acetate) to give 4-(4-bromophenyl)-cis-2,6-dimethylmorpholine (360 mg).

IR (KBr): 2971.8, 2871.5, 1821.3, 1494.6, 1452.1, 1241.9, 1176.4, 1145.5, 1085.7 cm^{-1}

NMR (CDCl_3 , δ): 1.25 (6H, d, $J=6.3\text{Hz}$), 2.39 (2H, t, $J=11.2\text{Hz}$), 3.39 (2H, d, $J=10.4\text{Hz}$), 3.7-3.9 (2H, m), 6.77 (2H, d, $J=9.0\text{Hz}$), 7.34 (2H, d, $J=9.0\text{Hz}$)

MASS (m/z): 270 (M^+)

The following compound was obtained according to a similar manner to that of Preparation 68.

Preparation 73

4-[4-(cis-2,6-Dimethylmorpholin-4-yl)phenyl]-2-methyl-3-butyne-2-ol

IR (KBr): 3326.6, 2979.5, 2931.3, 2873.4, 2832.9, 2223.5, 1606.4, 1511.9, 1454.1, 1376.9, 1334.5, 1238.1, 1174.4, 1151.3, 1081.9 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ): 1.14 (6H, d, $J=6.1\text{Hz}$), 1.44 (6H, s), 2.25 (2H, dd, $J=11.0$ and 12.3Hz), 3.5-3.8 (4H, m), 5.34 (1H, s), 6.90 (2H, d, $J=8.9\text{Hz}$), 7.21 (2H, d, $J=8.8\text{Hz}$)

MASS (m/z): 274 (M^++1)

The following compound was obtained according to a similar manner to that of Preparation 69.

Preparation 74

4-(4-Ethynylphenyl)-cis-2,6-dimethylmorpholine

IR (KBr): 3313.1, 2933.2, 2869.6, 2852.2, 2102.0, 1602.6, 1243.9, 1145.5, 1078.0 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ): 1.15 (6H, d, $J=6.1\text{Hz}$), 2.27 (2H, t,

J=11.7Hz), 3.6-3.8 (4H, m), 3.93 (1H, s), 6.91 (2H, d, J=8.9Hz), 7.30 (2H, d, J=8.8Hz)
MASS (m/z): 344 (M^+ +1)

- 5 The following compound was obtained according to a similar manner to that of Preparation 70.

Preparation 75

- 4-[5-[4-(cis-2,6-Dimethylmorpholin-4-yl)phenyl]isoxazol-3-yl]benzoic acid methyl ester

IR (KBr): 2973.7, 2873.4, 1718.3, 1614.1, 1510.0, 1450.2, 1278.6, 1241.9, 1178.3, 1106.9, 1089.6 cm^{-1}

- 15 NMR (CDCl_3 , δ): 1.18 (6H, d, J=6.1Hz), 2.36 (2H, t, J=11.0Hz), 3.6-3.9 (4H, m), 3.90 (3H, s), 7.11 (2H, d, J=8.9Hz), 7.48 (1H, s), 7.76 (2H, d, J=8.8Hz), 8.06 (2H, d, J=8.3Hz), 8.11 (2H, d, J=8.6Hz)

MASS (m/z): 393 (M^+ +1)

- 20 The following compound was obtained according to a similar manner to that of Preparation 71.

Preparation 76

- 25 4-[5-[4-(cis-2,6-Dimethylmorpholin-4-yl)phenyl]isoxazol-3-yl]benzoic acid

IR (KBr): 3430, 2975, 2857, 2652, 2530, 1689, 1614, 1508, 1450, 1240, 1176 cm^{-1}

- 30 NMR ($\text{DMSO}-d_6$, δ): 1.18 (6H, d, J=6.0Hz), 2.36 (2H, t, J=11.1Hz), 3.4-4.0 (5H, m), 7.11 (2H, d, J=8.9Hz), 7.46 (1H, s), 7.76 (2H, d, J=8.7Hz), 8.03 (2H, d, J=8.4Hz), 8.09 (2H, d, J=8.4Hz)

MASS (m/z): 379 (M^+ +1)

- The following compound was obtained according to a similar manner to that of Preparation 66.

Preparation 77

1-Bromo-4-(8-bromooctyloxy)benzene

IR (KBr): 1937.1, 2856.1, 1490.7, 1471.4, 1290.1,
1247.7, 1014.4 cm^{-1}

NMR (DMSO- d_6 , δ): 1.2-1.6 (8H, m), 1.6-2.0 (4H, m), 3.52
(2H, t, $J=6.7\text{Hz}$), 3.94 (2H, t, $J=6.4\text{Hz}$), 6.89 (2H,
d, $J=8.9\text{Hz}$), 7.42 (2H, d, $J=8.9\text{Hz}$)

10 The following compound was obtained according to a
similar manner to that of Preparation 67.

Preparation 78

4-[8-(4-Bromophenoxy)octyl]-cis-2,6-dimethylmorpholine

15 IR (KBr): 2933.2, 2867.6, 2850.3, 1490.7, 1471.4,
1238.1, 1145.5, 1076.1 cm^{-1}

NMR (DMSO- d_6 , δ): 1.02 (6H, d, $J=6.3\text{Hz}$), 1.2-1.8 (14H,
m), 2.1-2.3 (2H, m), 2.69 (2H, d, $J=10.4\text{Hz}$), 3.4-
3.6 (2H, m), 3.93 (2H, t, $J=6.4\text{Hz}$), 6.89 (2H, d,
20 $J=8.9\text{Hz}$), 7.42 (2H, d, $J=8.9\text{Hz}$)

MASS (m/z): 398 (M^+)

The following compound was obtained according to a
similar manner to that of Preparation 68.

25

Preparation 79

4-[4-[8-(cis-2,6-Dimethylmorpholin-4-
yl)octyloxy]phenyl]-2-methyl-3-butyn-2-ol

30 IR (KBr): 3187.8, 2973.7, 2933.2, 2858.0, 1602.6,
1506.1, 1469.5, 1241.9, 1164.8, 1139.7,
1081.9 cm^{-1}

NMR (DMSO- d_6 , δ): 1.02 (6H, d, $J=6.3\text{Hz}$), 1.2-1.8 (20H,
m), 2.1-2.3 (2H, m), 2.69 (2H, d, $J=10.4\text{Hz}$), 3.4-
3.7 (2H, m), 3.95 (2H, t, $J=6.4\text{Hz}$), 5.38 (1H, s),
35 6.89 (2H, d, $J=8.8\text{Hz}$), 7.29 (2H, d, $J=8.7\text{Hz}$)

MASS (m/z): 402 ($M^+ + 1$)

The following compound was obtained according to a similar manner to that of Preparation 69.

5

Preparation 80

4-[8-(4-Ethynylphenoxy)octyl]-cis-2,6-dimethylmorpholine

IR (KBr): 3313.1, 2933.2, 2869.6, 2852.2, 2102.0,
1602.6, 1243.9, 1145.5, 1078.0 cm^{-1}

10

NMR ($\text{DMSO}-d_6$, δ): 1.02 (6H, d, $J=6.3\text{Hz}$), 1.2-1.8 (14H, m), 2.1-2.3 (2H, m), 2.69 (2H, d, $J=10.4\text{Hz}$), 3.4-3.7 (2H, m), 3.97 (2H, t, $J=6.5\text{Hz}$), 4.00 (1H, s), 6.91 (2H, d, $J=8.7\text{Hz}$), 7.38 (2H, d, $J=8.7\text{Hz}$)

MASS (m/z): 344 ($M^+ + 1$)

15

The following compound was obtained according to a similar manner to that of Preparation 70.

Preparation 81

20

4-[5-[4-[8-(cis-2,6-Dimethylmorpholin-4-yl)octyloxy]phenyl]isoxazol-3-yl]benzoic acid methyl ester

IR (KBr): 2931.3, 2871.5, 2850.3, 1714.4, 1618.0,
1508.1, 1272.8 cm^{-1}

25

NMR (CDCl_3 , δ): 1.16 (6H, d, $J=6.3\text{Hz}$), 1.2-2.0 (14H, m), 2.2-2.4 (2H, m), 2.75 (2H, d, $J=10.5\text{Hz}$), 3.6-3.8 (2H, m), 3.96 (3H, s), 4.02 (2H, t, $J=6.5\text{Hz}$), 6.74 (1H, s), 6.99 (2H, d, $J=8.8\text{Hz}$), 7.77 (2H, d, $J=8.8\text{Hz}$), 7.94 (2H, d, $J=8.3\text{Hz}$), 8.15 (2H, d, $J=8.3\text{Hz}$)

30

MASS (m/z): 521 ($M^+ + 1$)

The following compound was obtained according to a similar manner to that of Preparation 71.

Preparation 82

4-[5-[4-[8-(cis-2,6-Dimethylmorpholin-4-yl)octyloxy]phenyl]isoxazol-3-yl]benzoic acid

IR (KBr): 3444.2, 2942.8, 2634.3, 2520.5, 1697.1,

5 1618.0 1452.1, 1278.6, 1259.3, 1180.2 cm^{-1}

NMR (CDCl_3 , δ): 1.12 (6H, d, $J=6.3\text{Hz}$), 1.2-1.9 (14H, m),
2.3-2.7 (2H, m), 2.8-3.2 (2H, m), 3.7-4.0 (2H, m),
4.0-4.2 (2H, m), 7.12 (2H, d, $J=8.8\text{Hz}$), 7.56 (1H,
s), 7.86 (2H, d, $J=8.7\text{Hz}$), 8.04 (2H, d, $J=8.5\text{Hz}$),
10 8.10 (2H, d, $J=8.5\text{Hz}$)

MASS (m/z): 493 ($M^+ + 1$)

The following compound was obtained according to a
similar manner to that of Preparation 67.

Preparation 83

1-Bromo-4-(7-methoxyheptyloxy)benzene

NMR ($\text{DMSO}-d_6$, δ): 1.2-1.6 (8H, m), 1.6-1.8 (2H, m), 3.20
(3H, s), 3.29 (2H, t, $J=6.4\text{Hz}$), 3.96 (2H, t,
20 $J=6.4\text{Hz}$), 5.39 (1H, s), 6.89 (2H, d, $J=8.8\text{Hz}$), 7.29
(2H, d, $J=8.8\text{Hz}$)

MASS (m/z): 301 (M^+)

The following compound was obtained according to a
25 similar manner to that of Preparation 68.

Preparation 84

4-[4-(7-Methoxyheptyloxy)phenyl]-2-methyl-3-butyn-2-ol

IR (KBr): 3394.1, 3309.2, 2979.5, 2939.0, 2871.5,

30 2852.2, 1606.4, 1510.0, 1469.5, 1247.7,
1160.9 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ): 1.2-1.6 (14H, m), 1.6-1.8 (2H, m),
3.20 (3H, s), 3.29 (2H, t, $J=6.4\text{Hz}$), 3.93 (2H, t,
 $J=6.5\text{Hz}$), 6.89 (2H, d, $J=9.0\text{Hz}$), 7.42 (2H, d,
35 $J=9.0\text{Hz}$)

MASS (m/z): 305.2 ($M^+ + 1$)

The following compound was obtained according to a similar manner to that of Preparation 69.

5

Preparation 85

1-Ethynyl-4-(7-methoxyheptyloxy)benzene

IR (KBr): 3313.1, 3290.0, 2935.1, 2859.9, 2105.9,
1606.4, 1506.1, 1247.7, 1114.7 cm^{-1}

10 NMR (DMSO- d_6 , δ): 1.2-1.6 (8H, m), 1.6-1.8 (2H, m), 3.20
(3H, s), 3.29 (2H, t, $J=6.4\text{Hz}$), 3.97 (2H, t,
 $J=6.5\text{Hz}$), 6.92 (2H, d, $J=8.9\text{Hz}$), 7.39 (2H, d,
 $J=8.8\text{Hz}$)

MASS (m/z): 247.2 ($M^+ + 1$)

15

The following compound was obtained according to a similar manner to that of Preparation 70.

Preparation 86

20 4-[5-[4-(7-Methoxyheptyloxy)phenyl]isoxazol-3-yl]benzoic
acid methyl ester

IR (KBr): 2935.1, 2861.8, 1720.2, 1618.0, 1436.7,
1276.6, 1112.7 cm^{-1}

25 NMR (CDCl_3 , δ): 1.2-1.7 (8H, m), 1.7-2.0 (2H, m), 3.34
(3H, s), 3.38 (2H, t, $J=6.5\text{Hz}$), 3.96 (3H, s), 4.02
(2H, t, $J=6.4\text{Hz}$), 6.75 (1H, s), 6.99 (2H, d,
 $J=8.9\text{Hz}$), 7.77 (2H, d, $J=8.8\text{Hz}$), 7.94 (2H, d,
 $J=8.5\text{Hz}$), 8.15 (2H, d, $J=8.4\text{Hz}$)

MASS (m/z): 424 ($M^+ + 1$)

30

The following compound was obtained according to a similar manner to that of Preparation 71.

Preparation 87

35 4-[5-[4-(7-Methoxyheptyloxy)phenyl]isoxazol-3-yl]benzoic

acid

IR (KBr): 2933.2, 2856.1, 2669.0, 2549.1, 1683.6,
1614.1, 1506.1, 1454.1, 1427.1, 1284.4, 1257.4,
1120.4 cm^{-1}

5 NMR (DMSO- d_6 , δ): 1.2-1.6 (8H, m), 1.7-1.9 (2H, m), 3.21
(3H, s), 3.2-3.5 (2H, m), 4.0-4.2 (2H, m), 7.0-7.2
(2H, m), 7.5 (1H, s), 7.8-8.0 (2H, m), 8.0-8.2 (4H,
m)

MASS (m/z): 410 ($M^+ + 1$)

10

The following compound was obtained according to a
similar manner to that of Preparation 66.

Preparation 88

15 1-Bromo-4-(7-bromoheptyloxy)benzene

IR (KBr): 2939.0, 2910.1, 2856.1, 1591.0, 1488.8,
1467.6, 1288.2, 1245.8 cm^{-1}

NMR (DMSO- d_6 , δ): 1.2-1.5 (6H, m), 1.6-1.9 (4H, m), 3.53
(2H, t, $J=6.7\text{Hz}$), 3.94 (2H, t, $J=6.5\text{Hz}$), 6.90 (2H,
20 d, $J=9.0\text{Hz}$), 7.42 (2H, d, $J=9.0\text{Hz}$)

MASS (m/z): 350 (M^+)

Preparation 89

A mixture of 1-bromo-4-(7-bromoheptyloxy)benzene (4.405
25 g), cis-2,6-dimethylmorpholine (1.55 ml) and potassium
carbonate (2.09 g) in N,N-dimethylformamide (22 ml) was
stirred for 1 hour at 70°C. To the reaction mixture was
added cis-2,6-dimethylmorpholine (7.75 ml) and stirred for 1
hour at 70°C. Ethyl acetate (100 ml) was added, and the
30 mixture washed with water (50 ml x 2) and brine. The
separated organic layer was dried over magnesium sulfate and
evaporated under reduced pressure to give a crude pale yellow
oil (5.30 g). The crude oil was purified by silica gel
chromatography (20:1-1:2 hexane-ethyl acetate) to give 4-[7-
35 (4-bromophenoxy)heptyl]-cis-2,6-dimethylmorpholine (4.43 g)

as a pale yellow oil.

IR (KBr): 2971.8, 2935.1, 2859.9, 2811.7, 2773.1,
1488.8, 1469.5, 1243.9, 1145.5, 1078 cm⁻¹

5 NMR (DMSO-d₆, δ): 1.02 (6H, d, J=6.3Hz), 1.2-1.8 (12H,
m), 2.1-2.3 (2H, m), 2.69 (2H, d, J=10.5Hz), 3.4-
3.6 (2H, m), 3.94 (2H, t, J=6.4Hz), 6.89 (2H, d,
J=8.9Hz), 7.42 (2H, d, J=8.9Hz)

MASS (m/z): 386 (M⁺+2)

10 The following compound was obtained according to a
similar manner to that of Preparation 68.

Preparation 90

15 4-[4-[7-(cis-2,6-Dimethylmorpholin-4-yl)heptyloxy]-
phenyl]-2-methyl-3-butyne-2-ol

IR (KBr): 3151.1, 2973.7, 2935.1, 2859.9, 2825.2,
1604.5, 1506.1, 1243.9, 1160.9, 1139.7 cm⁻¹

20 NMR (DMSO-d₆, δ): 1.02 (6H, d, J=6.3Hz), 1.2-1.8 (18H,
m), 2.1-2.3 (2H, m), 2.69 (2H, d, J=10.2Hz), 3.4-
3.7 (2H, m), 3.95 (2H, t, J=6.4Hz), 5.39 (1H, s),
6.89 (2H, d, J=8.7Hz), 7.28 (2H, d, J=8.6Hz)

MASS (m/z): 388 (M⁺+1)

25 The following compound was obtained according to a
similar manner to that of Preparation 69.

Preparation 91

30 4-[7-(4-Ethynylphenoxy)heptyl]-cis-2,6-
dimethylmorpholine

IR (KBr): 3290.0, 2971.8, 2935.1 2859.9, 2811.7,
2775.1, 2105.9, 1606.4, 1506.1, 1469.5, 1288.2,
1247.7, 1170.6, 1145.5, 1079.9, 833.1 cm⁻¹

35 NMR (DMSO-d₆, δ): 1.02 (6H, d, J=6.3Hz), 1.2-1.8 (12H,
m), 2.1-2.3 (2H, m), 2.69 (2H, d, J=10.3Hz), 3.4-
3.6 (2H, m), 3.95 (2H, t, J=6.5Hz), 4.00 (1H, s),

6.92 (2H, d, J=8.8Hz), 7.39 (2H, d, J=8.7Hz)

MASS (m/z): 330 ($M^+ + 1$)

- The following compound was obtained according to a
5 similar manner to that of Preparation 70.

Preparation 92

4-[5-[4-[7-(cis-2,6-Dimethylmorpholin-4-yl)heptyloxy]phenyl]isoxazol-3-yl]benzoic acid methyl ester.

- 10 IR (KBr): 2946.7, 2931.3, 2869.6, 2815.6, 2767.3,
1720.2, 1616.1, 1506.1, 1450.2, 1434.8, 1307.5,
1270.9, 1178.3, 1143.6, 1105.0 1078.0 cm^{-1}
NMR (CDCl_3 , δ): 1.16 (6H, d, J=6.3Hz), 1.2-2.0 (12H, m),
2.2-2.4 (2H, m), 2.75 (2H, d, J=10.4Hz), 3.5-3.9
15 (2H, m), 3.96 (3H, s), 4.02 (2H, t, J=6.5Hz), 6.75
(1H, s), 6.99 (2H, d, J=8.8Hz), 7.77 (2H, d,
J=8.8Hz), 7.94 (2H, d, J=8.5Hz), 8.15 (2H, d,
J=8.4Hz)
MASS (m/z): 507 ($M^+ + 1$)

20

The following compound was obtained according to a
similar manner to that of Preparation 71.

Preparation 93

- 25 4-[5-[4-[7-(cis-2,6-Dimethylmorpholin-4-yl)heptyloxy]-
phenyl]isoxazol-3-yl]benzoic acid
IR (KBr): 3446.2, 2939.0, 2636.2, 2520.5, 1693.2,
1618.0, 1508.1, 1452.1, 1265.1 cm^{-1}
NMR ($\text{DMSO}-d_6$, δ): 1.12 (6H, d, J=6.2Hz), 1.2-1.9 (12H,
30 m), 2.3-2.7 (2H, m), 2.8-3.2 (2H, m), 3.7-4.0 (2H,
m), 4.07 (2H, t, J=6.3Hz), 7.13 (2H, d, J=8.8Hz),
7.55 (1H, s), 7.86 (2H, d, J=8.5Hz), 8.04 (2H, d,
J=8.5Hz), 8.10 (2H, d, J=8.4Hz)
MASS (m/z): 507 ($M^+ + 1$)

35

Preparation 94

- To a solution of 4-hydroxypiperidine (15 g) in a mixture of tetrahydrofuran (THF) (150 ml) and water (100 ml) was added dropwise a solution of di-tert-butyl dicarbonate (48.5 g) in THF (100 ml) keeping pH 9 with 1N-sodium hydroxide under ice-cooling. The mixture was stirred at ambient temperature for 1 hour. The reaction mixture was successively washed with water and saturated sodium chloride, dried over anhydrous magnesium sulfate. Magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure to give crystals. The crystals were washed with n-hexane (300 ml), collected by filtration and dried in vacuo to give 1-N-t-butyloxycarbonyl-4-hydroxypiperidine (24.66 g).

Preparation 95

- To a solution of 1-N-t-butyloxycarbonyl-4-hydroxypiperidine (5.0 g) in dimethylformamide (DMF) (25 ml) was portionwise added sodium hydride (60% in oil) (1.29 g) with stirring under ice-cooling. The mixture was successively stirred at ambient temperature for 30 minutes, stirred at 60°C for 1 hour and cooled with an ice bath. To the reaction mixture was added 1,5-dibromopentane (6.72 ml), and the mixture was stirred at ambient temperature for 3 hours. The reaction solution was poured into water (100 ml) and extracted twice with a mixture of ethyl acetate (80 ml) and n-hexane (30 ml). The extract was washed with saturated aqueous sodium chloride, dried over magnesium sulfate and evaporated in vacuo. The resulting residue was chromatographed on silica gel (200 ml) eluting with a mixture of n-hexane and ethyl acetate (5:1 v/v). The fractions containing the desired compound were collected and evaporated under reduced pressure to give 4-(5-bromopentyloxy)-1-N-t-butyloxycarbonylpiperidine (2.44 g).
- NMR (CDCl₃, δ): 1.46 (9H, s), 1.50-1.70 (6H, m), 1.70-

1.96 (4H, m), 3.00-3.15 (2H, m), 3.35-3.50 (5H, m),
3.70-3.90 (2H, m)

APCI MASS (m/z): 250 (M^+ -101)

5 Preparation 96

To a solution of 4-(5-bromopentyloxy)-1-N-t-butylloxycarbonylpiperidine (2.44 g) in methanol (13 ml) was added 28% sodium methoxide methanol solution (14.2 ml), and the mixture was stirred under reflux for 4 hours. The reaction mixture was evaporated in vacuo. The resulting residue was chromatographed on silica gel (250 ml) eluting with a mixture of n-hexane and ethyl acetate (5:1 v/v). The fractions containing the object compound were collected and evaporated under reduced pressure to give 4-(5-methoxypentyloxy)-1-N-t-butylloxycarbonylpiperidine (1.97 g).

NMR ($CDCl_3$, δ): 1.45 (9H, s), 1.45-1.95 (10H, m), 3.03 (1H, dd, $J=3.47$ and 9.20 Hz), 3.10 (1H, dd, $J=3.47$ and 9.20 Hz), 3.44 (3H, s), 3.34-3.50 (5H, m), 3.70-3.85 (2H, m)

20 APCI MASS (m/z): 202 (M^+ -101)

Preparation 97

To a solution of 4-(5-methoxypentyloxy)-1-N-t-butylloxycarbonylpiperidine (1.97 g) in ethyl acetate (20 ml) was added 4N-hydrogen chloride ethyl acetate solution (16.3 ml), and the mixture was stirred at ambient temperature for 2 hours. The reaction mixture was evaporated in vacuo. The resulting residue was dissolved in a mixture of dichloromethane and methanol (10:1; 50 ml:5 ml). To this solution was added 1N-sodium hydroxide (5 ml) with stirring. The organic layer was separated and evaporated under reduced pressure to give 4-(5-methoxypentyloxy)piperidine (0.62 g).

NMR ($CDCl_3$, δ): 1.25-1.50 (2H, s), 1.50-1.75 (6H, m), 1.90-2.10 (2H, m), 2.70-2.90 (2H, m), 2.95-3.20 (2H, m), 3.33 (3H, s), 3.35-3.50 (5H, m)

APCI MASS (m/z): 202 (M^+)

Preparation 98

A solution of 4-fluorobenzonitrile (0.38 g), 4-(5-methoxy-pentyloxy)piperidine (0.62 g) and potassium carbonate (0.87 g) in DMF (8 ml) was stirred at 90-95°C for 6 hours. The reaction mixture was poured into water (50 ml) and extracted twice with a mixture of ethyl acetate and n-hexane (50 ml:20 ml). The extracts were combined, washed with saturated aqueous sodium chloride, dried over magnesium sulfate and evaporated in vacuo. The resulting residue was chromatographed on silica gel (100 ml) eluting with a mixture of n-hexane and ethyl acetate (5:1 v/v - 2:1 v/v). The fractions containing the desired compound were collected and evaporated under reduced pressure to give 4-(5-methoxy-pentyloxy)-N-(4-cyanophenyl)piperidine (294 mg).

NMR ($CDCl_3$, δ): 1.35-1.55 (2H, s), 1.55-1.75 (5H, m), 1.85-2.05 (2H, m), 3.13 (1H, dd, $J=3.47$ and 9.20Hz), 3.17 (1H, dd, $J=3.47$ and 9.20Hz), 3.33 (3H, s), 3.35-3.75 (8H, m), 6.85 (2H, d, $J=9.01$ Hz), 7.47 (2H, d, $J=8.96$ Hz)

APCI MASS (m/z): 303 (M^+)

Preparation 99

A solution of 4-(5-methoxy-pentyloxy)-N-(4-cyanophenyl)piperidine (294 mg) and thiosemicarbazide (0.68 g) in toluene (20 ml) and trifluoroacetic acid (10 ml) was stirred at 60-65°C for 7 hours. After cooling, the reaction mixture was poured into a mixture of water (100 ml) and ethyl acetate (200 ml) and adjusted to pH 10 with 1N-sodium hydroxide. The mixture was dissolved in a mixture of THF (50 ml) and methanol (10 ml). The organic layer was separated, washed with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate and evaporated in vacuo. The resulting precipitate was washed with isopropyl ether and

dried in vacuo to give 2-amino-5-[4-[4-(5-methoxypentyloxy)piperidin-1-yl]phenyl]-1,3,4-thiadiazole (1.29 g).

5 NMR (CDCl₃+CD₃OD, δ): 1.30-1.50 (2H, m), 1.50-1.80 (6H, m), 1.90-2.10 (2H, m), 2.90-3.10 (2H, m), 3.34 (3H, s), 3.35-3.70 (7H, m), 6.93 (2H, d, $J=8.91\text{Hz}$), 7.63 (2H, d, $J=8.83\text{Hz}$)

APCI MASS (m/z): 377 (M^+)

10 Preparation 100

To a suspension of 2-amino-5-[4-[4-(5-methoxypentyloxy)piperidin-1-yl]phenyl]-1,3,4-thiadiazole (1.29 g) in ethanol (20 ml) was added ethyl 4-bromoacetylbenzoate (1.39 g) and stirred at reflux for 5
15 hours. The reaction mixture was cooled and poured into diisopropyl ether (IPE) (60 ml). The resulting precipitate was collected by filtration and dried. To a suspension of the precipitate in xylene (40 ml) was added trifluoroacetic acid (4 ml), and the mixture was stirred at reflux (130°C)
20 for 5 hours. The reaction mixture was cooled and poured into IPE (300 ml). The resulting precipitate was filtered and dried to give 4-[2-[4-[4-(5-methoxypentyloxy)piperidin-1-yl]phenyl]imidazo[2,1-b][1,3,4]thiadiazol-6-yl]benzoic acid ethyl ester trifluoroacetic acid salt (2.01 g).

25 NMR (CDCl₃, δ): 1.42 (3H, t, $J=7.12\text{Hz}$), 1.45-1.75 (6H, m), 1.85-2.10 (2H, m), 2.30-2.50 (2H, m), 3.36 (3H, s), 3.35-3.55 (5H, m), 3.60-3.80 (2H, m), 4.40 (2H, q, $J=7.14\text{Hz}$), 7.57 (2H, d, $J=8.78\text{Hz}$), 7.84 (2H, d, $J=8.40\text{Hz}$), 7.91 (2H, d, $J=8.79\text{Hz}$), 8.13 (1H, s)

30 ESI MASS (m/z): 549 (M^++1)

Preparation 101

To a solution of 4-[2-[4-[4-(5-methoxypentyloxy)-piperidin-1-yl]phenyl]imidazo[2,1-b][1,3,4]thiadiazol-6-yl]benzoic acid ethyl ester trifluoroacetic acid salt (2.01 g)
35

- in a mixture of methanol (40 ml) and tetrahydrofuran (20 ml) was added 4N-NaOH (20 ml), and the mixture was refluxed for 6 hours. The reaction mixture was cooled, poured into water (200 ml) and adjusted to pH 2 with conc. HCl. The resulting
- 5 precipitate was collected by filtration, washed in turn with water, isopropyl alcohol (30 ml) and IPE (50 ml) to give 4-[2-[4-[4-(5-methoxypropyloxy)piperidin-1-yl]phenyl]imidazo[2,1-b][1,3,4]thiadiazol-6-yl]benzoic acid (1.28 g).
- 10 ESI MASS (m/z)(Negative): 519.2 ($M^+ + 1$)

Preparation 102

- To a solution of 4-[2-[4-[4-(5-methoxypropyloxy)-piperidin-1-yl]phenyl]imidazo[2,1-b][1,3,4]thiadiazol-6-yl]benzoic acid (1.28 g) and 1-hydroxybenzotriazole (465 mg)
- 15 in dichloromethane (50 ml) was added 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (WSCD-HCl) (943 mg), and the mixture was stirred overnight at ambient temperature. The reaction mixture was evaporated in vacuo.
- 20 To the resulting precipitate was added water (50 ml), and the solid was washed with water and IPE (50 ml) and dried under reduced pressure for 3 hours to give 4-[2-[4-[4-(5-methoxypropyloxy)piperidin-1-yl]phenyl]-imidazo[2,1-b][1,3,4]thiadiazol-6-yl]benzoic acid
- 25 benzotriazol-1-yl ester (1.26 g).

IR (KBr): 1774.2, 1708.6, 1604.5, 1471.4 1365.4, 1230.4 cm^{-1}

- NMR (CDCl_3 , δ): 1.30-1.80 (8H, m), 1.85-2.10 (2H, m), 3.05-3.30 (2H, m), 3.33 (3H, s), 3.35-3.55 (4H, m),
- 30 3.55-3.75 (2H, m), 6.94 (2H, d, $J=8.94\text{Hz}$), 7.30-7.60 (3H, m), 7.73 (2H, d, $J=8.79\text{Hz}$), 8.00-8.20 (4H, m), 8.30 (2H, d, $J=8.46\text{Hz}$)

ESI MASS (m/z)(Positive): 660.1 ($M^+ + \text{Na}$)

Preparation 103

To a solution of 4-hydroxy-N-(benzyloxycarbonyl)-piperidine (5.0 g) in THF (50 ml) were added 3-bromocyclohexene (3.67 ml) and silver oxide (7.4 g). The mixture was stirred at ambient temperature overnight. To the solution were added 3-bromocyclohexene (4.0 ml) and silver oxide (5.0 g), and the mixture was stirred at 40°C for 6 hours. The reaction mixture was filtered, and the filtrate was evaporated in vacuo. The resulting residue was chromatographed on silica gel (300 ml) eluting with a mixture of n-hexane and ethyl acetate (5:1 v/v). The fractions containing the desired compound were collected and evaporated under reduced pressure to give 4-(2-cyclohexenyloxy)-N-(benzyloxycarbonyl)piperidine (3.83 g).

NMR (CDCl_3 , δ): 1.40–2.20 (12H, m), 3.10–3.30 (2H, m), 3.50–3.70 (1H, m), 3.80–4.10 (3H, m), 5.12 (2H, s), 5.40–5.90 (2H, m), 7.35 (5H, m)

ESI MASS (m/z)(Positive): 338.3 ($\text{M}^+ + \text{Na}$)

Preparation 104

A solution of 4-(2-cyclohexenyloxy)-N-(benzyloxycarbonyl)piperidine (3.80 g), and 10% palladium on carbon (50% wet) (1.0 g) in methanol (40 ml) was hydrogenated under an atmospheric pressure of hydrogen at ambient temperature for 6 hours. The catalyst was filtered off, and the filtrate was evaporated in vacuo and dried in vacuo to give 4-(cyclohexyloxy)piperidine (2.42 g).

NMR (CDCl_3 , δ): 1.10–1.40 (4H, m), 1.40–2.00 (10H, m), 2.60–2.90 (2H, m), 3.05–3.20 (2H, m), 3.30–3.50 (1H, m), 3.50–3.75 (1H, m)

APCI MASS (m/z): 184.4 ($\text{M}^+ + 1$)

Preparation 105

A solution of 4-fluorobenzonitrile (1.50 g), 4-(cyclohexyloxy)piperidine (2.40 g) and potassium carbonate

- (3.3 g) in DMF (30 ml) was stirred at 90-95°C for 6 hours. The reaction mixture was poured into water (100 ml) and extracted twice with a mixture of ethyl acetate and n-hexane (80 ml:30 ml). The extracts were combined, washed with
- 5 saturated aqueous sodium chloride, dried over magnesium sulfate and evaporated in vacuo. The resulting residue was chromatographed on silica gel (200 ml) eluting with a mixture of n-hexane and ethyl acetate (6:1 v/v-5:1 v/v). The fractions containing the desired compound were collected and
- 10 evaporated under reduced pressure to give 4-[4-cyclohexyloxypiperidin-1-yl]benzonitrile (1.90 g).
- NMR (CDCl₃, δ): 1.10-1.40 (5H, m), 1.40-2.00 (9H, m),
3.00-3.20 (2H, m), 3.20-3.45 (1H, m), 3.55-3.80
(3H, m), 6.85 (2H, d, J=8.99Hz), 7.46 (2H, d,
15 J=8.95Hz)
- APCI MASS (m/z): 285 (M⁺)

Preparation 106

- A solution of 4-(4-cyclohexyloxypiperidin-1-yl)benzonitrile (1.90 g), thiosemicarbazide (0.91 g) in toluene (20 ml) and trifluoroacetic acid (10 ml) was stirred at 60-65°C with stirring for 7 hours. After cooling, the reaction mixture was poured into a mixture of water (100 ml) and ethyl acetate (100 ml) and adjusted to pH 10 with 1N-
- 25 sodium hydroxide. The mixture was dissolved in a mixture of THF (50 ml) and ethyl acetate (100 ml). The organic layer was separated, washed with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate and evaporated in vacuo. The resulting precipitate was washed diisopropyl
- 30 ether and dried in vacuo to give 2-amino-5-[4-[4-(cyclohexyloxy)piperidin-1-yl]phenyl]-1,3,4-thiadiazole (1.72 g).
- NMR (DMSO-d₆, δ): 1.10-1.45 (4H, m), 1.45-1.95 (10H, m),
2.85-3.10 (2H, m), 3.25-3.45 (1H, m), 3.50-3.80
35 (3H, m), 6.97 (2H, d, J=8.92Hz), 7.54 (2H, d,

J=8.80Hz)

APCI MASS (m/z): 360 (M^+ +1)

Preparation 107

- 5 To a suspension of 2-amino-5-[4-[4-(cyclohexyloxy)-piperidin-1-yl]phenyl]-1,3,4-thiadiazole (1.72 g) in ethanol (30 ml) was added ethyl 4-bromoacetylbenzoate (1.95 g) and the mixture was stirred at reflux for 5 hours. The reaction mixture was cooled and poured into IPE (60 ml). The
- 10 resulting precipitate was collected by filtration and dried. To a suspension of the precipitate in xylene (40 ml) was added trifluoroacetic acid (4 ml), and the mixture was stirred at reflux (130°C) for 5 hours. The reaction mixture was cooled and poured into IPE (300 ml). The resulting
- 15 precipitate was filtered and dried to give 4-[2-[4-[4-(cyclohexyloxy)piperidin-1-yl]phenyl]imidazo[2,1-b][1,3,4]-thiadiazol-6-yl]benzoic acid ethyl ester trifluoroacetic acid salt (2.01 g). This compound was immediately used as the starting compound for the next step.

20

The following compound was obtained according to a similar manner to that of Preparation 101.

Preparation 108

- 25 4-[2-[4-[4-(Cyclohexyloxy)piperidin-1-yl]phenyl]imidazo[2,1-b][1,3,4]thiadiazol-6-yl]benzoic acid
- NMR ($CDCl_3+CD_3OD$, δ): 1.10-2.10 (14H, m), 2.90-3.20 (2H, m), 4.20-4.60 (1H, m), 6.96 (2H, d, J=8.24Hz), 7.50-8.20 (7H, m)
- 30 ESI MASS (m/z): 525.3 (M^+ +Na)

The following compound was obtained according to a similar manner to that of Preparation 102.

Preparation 109

4-[2-[4-[4-(Cyclohexyloxy)piperidin-1-yl]phenyl]-imidazo[2,1-b][1,3,4]thiadiazol-6-yl]benzoic acid benzotriazol-1-yl ester

5 IR (KBr): 1772, 1703, 1606, 1470, 1369 cm^{-1}

Preparation 110

To a solution of 4-(4-methanesulfonyloxypiperidin-1-yl)benzonitrile (4.90 g) in N,N-dimethylformamide (DMF) (50 ml) were added potassium carbonate (4.83 g) and 2,6-dimethylmorpholine (3.02 g), and the mixture was stirred at 90-95°C for 6 hours. After cooling, the reaction mixture was poured into water (300 ml) and extracted twice with a mixture of ethyl acetate and n-hexane (100 ml:30 ml). The extracts were combined and washed in turn with water and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate and evaporated in vacuo. The resulting precipitates were washed with IPE (100 ml), collected by filtration and dried in vacuo to give 4-[4-(2,6-dimethylmorpholin-4-yl)piperidin-1-yl]benzonitrile (2.29 g).

NMR (CDCl_3 , δ): 1.18 (6H, d, $J=6.03\text{Hz}$), 1.60-1.90 (2H, m), 1.90-2.15 (2H, m), 2.35-2.60 (2H, m), 3.10-3.30 (2H, m), 3.40-4.10 (6H, m), 4.80-5.05 (1H, m), 6.87 (2H, d, $J=8.97\text{Hz}$), 7.48 (2H, d, $J=8.96\text{Hz}$)

25 APCI MASS (m/z): 300 (M^+)

The following compound was obtained according to a similar manner to that of Preparation 99.

Preparation 111

2-Amino-5-[4-[4-(2,6-dimethylmorpholin-4-yl)piperidin-1-yl]phenyl]-1,3,4-thiadiazole

NMR (CDCl_3 , δ): 1.19 (6H, d, $J=6.22\text{Hz}$), 1.70-2.15 (4H, m), 3.10-3.25 (2H, m), 3.40-3.70 (4H, m), 3.70-4.10 (2H, m), 4.80-5.00 (1H, m), 6.94 (2H, d, $J=8.88\text{Hz}$),

7.65 (2H, d, J=8.82Hz)

APCI MASS (m/z): 374 (M⁺)

The following compound was obtained according to a
5 similar manner to that of Preparation 100.

Preparation 112

4-[2-[4-[4-(2,6-Dimethylmorpholin-4-yl)piperidin-1-
yl]phenyl]imidazo[2,1-b][1,3,4]thiadiazol-6-yl]benzoic acid
10 ethyl ester trifluoroacetic acid salt.

NMR (CDCl₃, δ): 1.19 (6H, d, J=6.20Hz), 1.41 (3H, t,
J=7.11Hz), 1.70-1.90 (2H, m), 1.90-2.20 (2H, m),
2.40-2.65 (2H, m), 3.20-3.40 (2H, m), 3.40-4.30
(8H, m), 4.39 (2H, q, J=7.07Hz), 4.85-5.10 (1H, m),
15 7.02 (2H, d, J=8.93Hz), 7.76 (2H, d, J=8.81Hz),
7.87 (2H, d, J=8.34Hz), 8.08 (1H, s), 8.11 (2H, d,
J=9.71Hz)

The following compound was obtained according to a
20 similar manner to that of Preparation 101.

Preparation 113

4-[2-[4-[4-(2,6-Dimethylmorpholin-4-yl)piperidin-1-
yl]phenyl]imidazo[2,1-b][1,3,4]thiadiazol-6-yl]benzoic acid
25 APCI MASS (m/z): 519 (M⁺+1)

The following compound was obtained according to a
similar manner to that of Preparation 102.

30 Preparation 114

4-[2-[4-[4-(2,6-Dimethylmorpholin-4-yl)piperidin-1-
yl]phenyl]imidazo[2,1-b][1,3,4]thiadiazol-6-yl]benzoic acid
benzotriazol-1-yl ester

IR (KBr): 1774, 1691, 1605, 1466, 1429, 1232 cm⁻¹
35

Preparation 115

A solution of 4-[4-(methanesulfonyloxy)piperidin-1-yl]nitrobenzene (2.0 g), and potassium thioacetate (1.14 g) in dimethylsulfoxide (DMSO) (20 ml) was stirred at 100-110°C for 3 hours. The reaction mixture was poured into water (100 ml) and extracted twice with ethyl acetate (100 ml). The extracts were collected, washed with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate and evaporated in vacuo. The resulting precipitates were washed with IPE (50 ml), collected by filtration and dried in vacuo to give 4-(4-acetylthiopiperidin-1-yl)nitrobenzene (1.15 g).

NMR (CDCl₃, δ): 1.60-1.85 (2H, m), 2.00-2.20 (2H, m), 2.34 (3H, s), 3.15-3.35 (2H, m), 3.65-3.90 (3H, m), 6.81 (2H, d, J=9.47Hz), 8.12 (2H, d, J=9.43Hz)

APCI MASS (m/z): 281 (M⁺)

Preparation 116

To a solution of 4-(4-acetylthiopiperidin-1-yl)nitrobenzene (3.34 g) in a mixture of THF (30 ml) and methanol (30 ml) was added 28% sodium methoxide methanol solution (2.67 ml) at 0-5°C and stirred at the same temperature for 30 minutes. To the mixture was added iodopropane (1.51 ml) at the same temperature and stirred at ambient temperature for 2 hours. The reaction mixture was evaporated in vacuo and dissolved in ethyl acetate (100 ml). The solution was washed three times with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate and evaporated in vacuo. A solution of the resulting residue, ammonium chloride (1.0 g) and iron powder (4.0 g) in a mixture of ethanol (60 ml) and water (30 ml) was refluxed for 2 hours. The reaction mixture was evaporated in vacuo. The resulting residue was chromatographed on silica gel (300 ml) eluting with ethyl acetate. The fractions containing the desired compound were collected and evaporated under reduced pressure to give 4-(4-propylthiopiperidin-1-yl)aniline (2.47

g).

NMR (CDCl_3 , δ): 1.00 (3H, t, $J=7.16\text{Hz}$), 1.50-1.90 (4H, m), 1.95-2.15 (2H, m), 2.55 (2H, t, $J=7.56\text{Hz}$), 2.60-2.80 (3H, m), 3.35-3.55 (4H, m), 6.63 (2H, d, $J=8.81\text{Hz}$), 6.81 (2H, d, $J=8.80\text{Hz}$)

APCI MASS (m/z): 251 (M^+)

Preparation 117

A solution of 4-(4-propylthiopiperidin-1-yl)aniline (2.44 g), 1-[2-(p-toluenesulfonyloxy)ethyl]-2-oxazolidone (3.08 g) and potassium carbonate (3.28 g) in a mixture of acetonitrile (25 ml) and DMF (13 ml) was stirred at 120°C for 5 hours. The reaction mixture was poured into water (100 ml) and extracted twice with ethyl acetate (60 ml). The extracts were collected, washed twice with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate and evaporated in vacuo. The resulting residue was chromatographed on silica gel (200 ml) eluting with ethyl acetate. The fractions containing the desired compound were collected and evaporated under reduced pressure to give 1-[(2-oxazolidon-3-yl)ethylamino]-4-[4-(propylthio)piperidin-1-yl]benzene (1.98 g).

NMR (CDCl_3 , δ): 1.00 (3H, t, $J=7.34\text{Hz}$), 1.50-1.90 (5H, m), 2.00-2.20 (2H, m), 2.55 (2H, t, $J=7.5\text{Hz}$), 2.55-2.90 (3H, m), 3.10-3.65 (8H, m), 4.29 (2H, dd, $J=6.56$ and 8.29Hz), 6.40-6.70 (2H, m), 6.70-6.95 (2H, m)

APCI MASS (m/z): 364 (M^+)

Preparation 118

A solution of 1-[(2-oxazolidon-3-yl)ethylamino]-4-(4-propylthiopiperidin-1-yl)benzene (1.96 g) in 30% HBr in acetic acid solution (15 ml) was stirred at ambient temperature overnight. IPE (100 ml) was added to the reaction mixture, and the resulting precipitates were

collected by filtration, washed with IPE (40 ml) and dried under reduced pressure. The precipitates were dissolved in a mixture of ethanol (20 ml) and n-butylalcohol (40 ml), and the solution was refluxed for 6 hours. After cooling, to the reaction mixture was added IPE (100 ml), and the resulting precipitates were collected by filtration, washed with IPE (20 ml) and dried in vacuo to give 1-[4-(4-propylthiopiperidin-1-yl)phenyl-1-yl]piperazine (2.51 g).

NMR ($\text{CDCl}_3 + \text{CD}_3\text{OD}$, δ): 1.03 (3H, t, $J=6.98\text{Hz}$), 1.50-1.90 (2H, m), 2.10-2.40 (3H, m), 2.50-2.90 (5H, m), 6.80-7.00 (2H, m), 7.55-7.70 (2H, m)

APCI MASS (m/z): 320 (M^+)

Preparation 119

A solution of 1-[4-(4-propylthiopiperidin-1-yl)benzen-1-yl]piperazine (2.45 g) and potassium carbonate (2.81 g) in N,N-dimethylsulfoxide (30 ml) was stirred at 100°C for 30 minutes and then at 150°C for 5 hours. The reaction mixture was poured into water (100 ml) and extracted twice with ethyl acetate (100 ml). The extracts were collected, washed twice with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate and evaporated in vacuo. The resulting residue was chromatographed on silica gel (200 ml) eluting with a mixture of dichloromethane and methanol (9:1 v/v). The fractions containing the desired compound were collected and evaporated under reduced pressure and washed with IPE. The precipitates were collected by filtration and dried in vacuo to give 4-[1-[4-(4-propylthiopiperidin-1-yl)phenyl]piperazin-4-yl]benzoic acid ethyl ester (1.22 g).

NMR (CDCl_3 , δ): 1.01 (3H, t, $J=7.36\text{Hz}$), 1.37 (3H, t, $J=7.79\text{Hz}$), 1.50-1.90 (4H, m), 2.00-2.20 (2H, m), 2.56 (2H, t, $J=7.53\text{Hz}$), 2.65-2.90 (3H, m), 3.15-3.30 (4H, m), 3.40-3.60 (6H, m), 4.33 (2H, q, $J=7.11\text{Hz}$), 6.91 (2H, d, $J=9.10\text{Hz}$), 6.92 (4H, s), 7.95 (2H, d, $J=8.97\text{Hz}$)

APCI MASS (m/z): 468 (M⁺)

Preparation 120

To a solution of 4-[1-[4-(4-propylthiopiperidin-1-yl)phenyl]piperazin-4-yl]benzoic acid ethyl ester (1.22 g) in a mixture of ethanol (10 ml) and tetrahydrofuran (40 ml) was added 10% aqueous NaOH (2.1 ml) and 1N-NaOH (10 ml), and the mixture was refluxed for 6 hours. The reaction mixture was cooled and adjusted to pH 2.5-3.0 with 1N-HCl. The resulting precipitates were collected by filtration, washed in turn with water (30 ml) and IPE (50 ml) and dried in vacuo to give 4-[1-[4-(4-propylthiopiperidin-1-yl)phenyl]piperazin-4-yl]benzoic acid (0.99 g).

NMR (DMSO-d₆, δ): 0.94 (3H, t, J=7.38Hz), 1.40-1.70 (5H, m), 1.85-2.15 (2H, m), 2.60-2.90 (4H, m), 3.00-3.20 (5H, m), 3.30-3.55 (6H, m), 6.88 (4H, s), 7.01 (2H, d, J=9.00Hz), 7.78 (2H, d, J=8.89Hz)

APCI MASS (m/z): 440 (M⁺)

Preparation 121

To a solution of 4-[1-[4-(4-propylthiopiperidin-1-yl)phenyl]piperazin-4-yl]benzoic acid (0.98 g), 1-hydroxybenzotriazole (0.39 g) in dichloromethane (20 ml) was added 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (WSCD-HCl) (0.85 g), and the mixture was stirred for 15 minutes. To the solution was added triethylamine (0.31 ml), and the mixture was stirred overnight at ambient temperature. The reaction mixture was poured into a mixture of 0.1N-hydrochloric acid (25 ml) and dichloromethane (60 ml). The organic layer was washed with water and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate and evaporated in vacuo. To the resulting precipitates were washed with water and IPE (50 ml), collected by filtration and dried under reduced pressure to give 4-[1-[4-(4-propylthiopiperidin-1-yl)phenyl]piperazin-

4-yl]benzoic acid benzotriazol-1-yl ester (1.04 g).

NMR (CDCl₃, δ): 1.01 (3H, t, J=7.36Hz), 1.50-1.90 (5H, m), 2.00-2.20 (2H, m), 2.56 (2H, t, J=7.56Hz), 2.65-2.90 (3H, m), 3.20-3.30 (4H, m), 3.45-3.70 (6H, m), 6.94 (4H, s), 7.00 (2H, d, J=9.19Hz), 7.35-7.60 (3H, m), 8.05-8.20 (3H, m)

APCI MASS (m/z): 557 (M⁺)

Preparation 122

To a solution of N-t-butyloxycarbonyl-4-acetylthiopiperidine (5.5 g) in a mixture of THF (50 ml) and methanol (50 ml) was added 28% sodium methoxide methanol solution (4.76 ml) with stirring under ice-cooling and stirred at the same temperature for 30 minutes. To the solution was added 1,6-dibromohexane (17.1 g) under ice-cooling, and the mixture was successively stirred at ambient temperature for 30 minutes and then stirred at 45°C for 2 hours. The reaction mixture was concentrated in vacuo. The resulting residue was chromatographed on silica gel (500 ml) eluting with a mixture of n-hexane and ethyl acetate (6:1 v/v). The fractions containing the desired compound were collected and evaporated under reduced pressure to give 4-(6-bromohexylthio)-N-t-butyloxycarbonylpiperidine (4.95 g).

NMR (CDCl₃, δ): 1.45 (9H, s), 1.45-1.70 (8H, m), 1.80-2.00 (4H, m), 2.55 (1H, t, J=7.34Hz), 2.65-3.05 (3H, m), 3.30-3.50 (2H, m), 3.85-4.10 (2H, m)

APCI MASS (m/z): 250 (M⁺-101)

Preparation 123

To a solution of 4-(6-bromohexylthio)-N-t-butyloxycarbonylpiperidine (4.95 g) in methanol (20 ml) was added 28% sodium methoxide methanol solution (26.6 ml), and the mixture was stirred under reflux for 4 hours. After cooling, the reaction mixture was evaporated in vacuo. The resulting residue was chromatographed on silica gel (400 ml)

eluting with a mixture of n-hexane and ethyl acetate (5:1 v/v). The fractions containing the object compound were collected and evaporated under reduced pressure to give 4-(6-methoxyhexylthio)-N-t-butyloxycarbonylpiperidine (3.32 g).

- 5 NMR (CDCl_3 , δ): 1.25-1.45 (6H, m), 1.45 (9H, s), 1.45-1.60 (4H, m), 1.80-2.00 (2H, m), 2.54 (2H, t, $J=7.47\text{Hz}$), 2.60-3.00 (3H, m), 3.30 (3H, s), 3.37 (2H, t, $J=6.34\text{Hz}$), 3.96 (2H, m)

10 Preparation 124

- To a solution of 4-(6-methoxyhexylthio)-N-t-butyloxycarbonylpiperidine (3.32 g) in dichloromethane (40 ml) were added triethylsilane (8.0 ml) and trifluoroacetic acid (15.4 ml) with stirring in an ice bath. The mixture was
15 stirred at ambient temperature for 2 hours. The reaction mixture was evaporated in vacuo. The resulting residue was chromatographed on silica gel (400 ml) eluting with a mixture of dichloromethane and methanol (4:1 v/v). The fractions containing the object compound were collected and evaporated
20 under reduced pressure to give 4-(6-methoxyhexylthio)-piperidine (4.77 g). This compound was immediately used as the starting compound for the next step.

- NMR (CD_3OD , δ): 1.30-1.90 (10H, m), 2.10-2.30 (2H, m),
2.60 (2H, t, $J=7.30\text{Hz}$), 3.31 (3H, s), 3.42 (2H, t, $J=4.28\text{Hz}$)
25 APCI MASS (m/z): 232.4 (M^++1)

The following compound was obtained according to a similar manner to that of Preparation 98.

30

Preparation 125

4-(6-Methoxyhexylthiopiperidin-1-yl)benzonitrile

- NMR (CDCl_3 , δ): 1.30-1.50 (4H, m), 1.50-1.80 (6H, m),
1.95-2.15 (2H, m), 2.57 (2H, t, $J=7.50\text{Hz}$), 2.75-
35 3.10 (3H, m), 3.33 (3H, s), 3.37 (2H, t, $J=6.32\text{Hz}$),

3.65-3.90 (2H, m), 6.84 (2H, d, J=9.08Hz), 7.47
(2H, d, J=9.08Hz)

APCI MASS (m/z): 347 (M⁺)

- 5 The following compound was obtained according to a similar manner to that of Preparation 99.

Preparation 126

- 10 2-Amino-5-[4-[4-(6-methoxyhexylthio)piperidin-1-yl]-phenyl]-1,3,4-thiadiazole

NMR (DMSO-d₆, δ): 1.20-1.60 (10H, m), 1.85-2.05 (2H, m),
2.45-2.60 (2H, m), 2.80-3.00 (3H, m), 3.21 (3H, s),
3.29 (2H, t, J=6.42Hz), 3.60-3.80 (2H, m), 6.97
(2H, d, J=8.94Hz), 7.20 (2H, s), 7.55 (2H, d,
J=8.80Hz)

15 APCI MASS (m/z): 421 (M⁺)

The following compound was obtained according to a similar manner to that of Preparation 100.

20

Preparation 127

4-[2-[4-[4-(6-Methoxyhexylthio)piperidin-1-yl]-phenyl]imidazo[2,1-b][1,3,4]thiadiazol-6-yl]benzoic acid ethyl ester trifluoroacetic acid salt

- 25 ESI MASS (m/z)(Positive): 579 (M⁺)

The following compound was obtained according to a similar manner to that of Preparation 101.

- 30 Preparation 128

4-[2-[4-[4-(6-Methoxyhexylthio)piperidin-1-yl]-phenyl]imidazo[2,1-b][1,3,4]thiadiazol-6-yl]bezoic acid

NMR (CDCl₃, δ): 1.30-1.80 (10H, m), 1.95-2.25 (2H, m),
2.45-2.70 (2H, m), 2.70-3.20 (4H, m), 3.35 (3H, s),
3.35-3.50 (2H, m), 6.80-7.05 (3H, m), 7.36 (1H, s),

35

7.63 (1H, d, J=8.19Hz), 7.75 (1H, d, J=8.21Hz),
7.89 (1H, d, J=7.52Hz), 8.00-8.20 (2H, m)

APCI MASS (m/z): 551 (M⁺)

- 5 The following compound was obtained according to a similar manner to that of Preparation 102.

Preparation 129

- 4-[2-[4-[4-(6-Methoxyhexylthio)piperidin-1-yl]-phenyl]imidazo[2,1-b][1,3,4]thiadiazol-6-yl]benzoic acid
benzotriazol-1-yl ester

IR (KBr): 1772, 1603, 1535, 1470 cm⁻¹

Preparation 130

- 15 To a solution of tetrahydrothiopyran-4-one (1.0 g) in dichloromethane (20 ml) was added 3-chloroperoxybenzoic acid (4.16 g, purity 80%) under ice-cooling with stirring. The mixture was stirred at the same temperature for 20 minutes and then stirred at ambient temperature for 1 hour. The
20 resulting precipitates were filtered off, and the filtrate was concentrated in vacuo. The residue was dissolved in a mixture of ethyl acetate (50 ml) and water (20 ml) and adjusted to pH 2 with 1N-hydrochloric acid. The organic layer was separated, and the aqueous layer was extracted with ethyl
25 acetate (50 ml). The organic layers were combined, washed in turn with water, saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate and evaporated in vacuo. The resulting residue was dissolved in a mixture of dichloromethane (100
30 ml) and methanol (20 ml), dried over anhydrous magnesium sulfate and evaporated in vacuo to give 1,1-dioxotetrahydrothiopyran-4-one (1.18 g).

NMR (CD₃CD, δ): 2.20 (4H, t, J=6.05Hz),
2.90-3.20 (4H, m)

Preparation 131

To a solution of (R,S)-5-hydroxy-2-phenyl-1,3-dioxane (5.0 g) (Acta Chemica Scandinavia, 1996; 50: 185-187) in DMF (50 ml) were added t-butyl dimethylsilyl chloride (12.5 g) and imidazole (9.45 g) with stirring at ambient temperature, and the mixture was allowed to stand at the same temperature overnight. The reaction mixture was poured into pH 6.86 standard buffer solution (500 ml) and extracted twice with ethyl acetate (200 ml). The extracts were combined, washed successively with water and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate and evaporated in vacuo. The resulting residue was chromatographed on silica gel (400 ml) eluting with a mixture of n-hexane and ethyl acetate (9:1 v/v). The fractions containing the object compound were collected and evaporated under reduced pressure to give (R,S)-5-(tert-butyl dimethylsilyloxy)-2-phenyl-1,3-dioxane (10.14 g).

NMR (CDCl_3 , δ): 0.02-0.12 (6H, m), 0.89-0.94 (9H, m), 3.50-4.25 (5H, m), 5.50-5.95 (1H, m), 7.30-7.55 (5H, m)

ESI MASS (m/z) (Positive): 317.3 ($\text{M}^+ + \text{Na}$)

Preparation 132

A solution of (R,S)-5-tert-butyl dimethylsilyloxy-2-phenyl-1,3-dioxane (10.1g) and 10% palladium on carbon (50% including water) (5.0 g) in methanol (100 ml) was hydrogenated under an atmospheric pressure of hydrogen with stirring at ambient temperature for 2 hours. The catalyst was filtered off, and the filtrate was dried over anhydrous magnesium sulfate and evaporated in vacuo. The resulting residue was chromatographed on silica gel (300 ml), eluting with a mixture of n-hexane and ethyl acetate (3:1 v/v). The fractions containing the object compound were collected and evaporated under reduced pressure to give (R,S)-2-(tert-butyl dimethylsilyloxy)-3-hydroxypropanol (5.69 g). This

compound was immediately used as the starting compound for the next step. To a solution of this compound were successively added diisopropylethylamine (14.4 ml) and acetyl chloride (6.5 ml) with stirring, and the mixture was stirred at 0-5°C for 2 hours. Water (10 ml) was added to the reaction mixture, and the organic layer was separated, washed with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate and evaporated in vacuo. The resulting residue was dissolved in a mixture of methanol (100 ml) and conc. hydrochloric acid (1.0 ml), and the solution was stirred at ambient temperature for 2 hours. The reaction mixture was concentrated in vacuo and chromatographed on silica gel (200 ml) eluting with a mixture of n-hexane and ethyl acetate (2:1 v/v). The fractions containing the object compound were collected and evaporated under reduced pressure to give (R,S)-2-hydroxy-1,3-diacetoxyp propane (2.06 g).

NMR (CDCl₃, δ): 2.06 (3H, s), 2.11 (3H, s), 3.74 (1H, m), 4.10-4.25 (4H, m)

20 Preparation 133

To a solution of oxalyl chloride (1.09 ml) in dichloromethane (20 ml) was added dropwise dimethylsulfoxide (DMSO) (1.93 ml) with stirring at -40~-50°C. After stirring at the same temperature for 5 minutes, to the solution was added dropwise a solution of (R,S)-2-hydroxy-1,3-diacetoxyp propane (2.0 g) in dichloromethane (20 ml) and stirred at the same temperature for 30 minutes. Triethylamine (5.54 ml) was added dropwise to the reaction mixture with stirring at the same temperature, and then the mixture was stirred at ambient temperature for 30 minutes. The insoluble material was filtered off, and the filtrate was washed successively with 0.5N hydrochloric acid, water, saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate and evaporated in vacuo. The resulting residue was

chromatographed on silica gel (200 ml) eluting with a mixture of n-hexane and ethyl acetate (1:2 v/v). The fractions containing the object compound were collected and evaporated under reduced pressure to give 2-oxo-1,3-diacetoxyp propane

5 (1.17 g).

NMR (CDCl₃, δ): 2.18 (6H, s), 4.76 (4H, s)

ESI MASS (m/z)(Positive): 197.3 (M⁺+Na)

Preparation 134

10 To a solution of (R,S)-5-hydroxy-2-phenyl-1,3-dioxane (10.0 g) (Acta Chemica Scandinavica, 1996; 50: 185-187) in dichloromethane (200 ml) were added molecular sieves 4A powder (28 g) and pyridinium chlorochromic acid (PCC) (23.9 g) with stirring at ambient temperature and the mixture was stirred at the same temperature for 2 hours. To the reaction mixture was added diethyl ether (100 ml), and the insoluble material was filtered off with celite and the filtrates were evaporated in vacuo. The residue was dissolved in a mixture of n-hexane (100 ml) and ethyl acetate (100 ml), dried over anhydrous magnesium sulfate and evaporated in vacuo. The resulting residue was chromatographed on silica gel (600 ml) eluting with a mixture of n-hexane and ethyl acetate (2:1 v/v). The fractions containing the object compound were collected and evaporated under reduced pressure to give 5-oxo-2-phenyl-1,3-dioxane (7.06 g).

NMR (CDCl₃, δ): 4.49 (2H, s), 4.50 (2H, s), 5.90 (1H, s), 7.30-7.60 (5H, m)

Preparation 135

30 To a solution of 4-aminobutanol (630 mg), 5-oxo-2,2-dimethyl-1,3-dioxane (1.0 g) and acetic acid (1.20 ml) in MeOH (9 ml)-DMF (4 ml) was added sodium cyanoborohydride (622 mg) with stirring at ambient temperature, and the mixture was stirred at the same temperature overnight. To the reaction mixture was added dropwise a solution of allyloxycarbonyl

chloride (0.97 ml) in THF (2 ml) with stirring under ice-cooling, and the mixture was stirred at the same temperature for 1 hour. To the reaction mixture were added ethyl acetate (50 ml) and n-hexane (10 ml), and the solution was washed in turn with water and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate and evaporated in vacuo. The resulting residue was chromatographed on silica gel (100 ml) eluting with a mixture of n-hexane and ethyl acetate (1:1 v/v). The fractions containing the object compound were collected and evaporated under reduced pressure to give 4-[allyloxycarbonyl-(2,2-dimethyl-1,3-dioxan-5-yl)]aminobutanol (1.04 g).

NMR (CDCl₃, δ): 1.42 (3H, s), 1.48 (3H, s), 1.50-1.80 (4H, m), 3.45 (2H, t, J=8.20Hz), 3.68 (2H, ABq, J=5.84 and 11.36Hz), 3.80-4.20 (5H, m), 4.50-4.70 (2H, m), 5.15-5.40 (2H, m), 5.80-6.05 (1H, m)

ESI MASS (m/z)(Positive): 310.3 (M⁺+Na)

Preparation 136

To a solution of oxalyl chloride (0.32 ml) in dichloromethane (10 ml) was added DMSO (0.57 ml) dropwise with stirring at -40~-50°C. After stirring at the same temperature for 5 minutes, to the solution was added dropwise a solution of 4-[allyloxycarbonyl(2,2-dimethyl-1,3-dioxan-5-yl)]aminobutanol (1.0 g) in dichloromethane (5 ml) and stirred at the same temperature for 30 minutes. Triethylamine (1.46 ml) was added dropwise to the reaction mixture with stirring at the same temperature, and then the mixture was stirred at ambient temperature for 30 minutes. The insoluble material was filtered off, and the filtrate was washed successively with 1N-hydrochloric acid, water, saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate and evaporated in vacuo. The resulting residue was dissolved in a mixture of acetic acid (16 ml) and water (4 ml), and the

solution was stirred at 90~100°C for 5 hours. The reaction mixture was concentrated in vacuo. The resulting residue was chromatographed on silica gel (100 ml) eluting with a mixture of dichloromethane and methanol (19:1 v/v). The fractions containing the object compound were collected and evaporated under reduced pressure to give 4-[allyloxycarbonyl-(1,3-dihydropropan-2-yl)]aminobutylaldehyde (321 mg).

NMR (CDCl₃, δ): 1.50-1.75 (2H, m), 1.80-2.00 (2H, m), 2.40-2.60 (2H, m), 3.20-4.10 (7H, m), 4.59 (2H, d, J=5.60Hz), 5.10-5.40 (2H, m), 5.80-6.10 (1H, m)
APCI MASS (m/z)(Positive): 246 (M⁺)

The following compound was obtained according to a similar manner to that of Preparation 95.

Preparation 137

N-t-Butoxycarbonyl-4-allyloxypiperidine

NMR (CDCl₃, δ): 1.45 (9H, s), 1.45-1.60 (2H, m), 1.70-1.95 (2H, m), 3.00-3.20 (2H, m), 3.40-3.60 (1H, m), 3.65-3.90 (2H, m), 3.95-4.05 (2H, m), 5.10-5.35 (2H, m), 5.80-6.10 (1H, m)

Preparation 138

To a solution of N-t-butoxycarbonyl-4-allyloxypiperidine (2.95 g) in THF (15 ml) was added 9-borobicyclo[3.3.1]nonane (9-BBN, 0.5M solution in THF) (51.3 ml) under ice-cooling with stirring, and the mixture was stirred at ambient temperature for 4 hours. The reaction mixture was cooled at 0-5°C, and 3M aqueous sodium hydroxide (20.4 ml) and 30% hydrogen peroxide aqueous solution (20.4 ml) were added the reaction mixture at 0-5°C. The mixture was stirred at ambient temperature for 1 hour. To a reaction mixture was added ethyl acetate (100 ml), and the solution was washed successively with saturated aqueous sodium chloride, 1N-hydrochloric acid, saturated aqueous sodium bicarbonate and

saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate and evaporated in vacuo. The resulting residue was chromatographed on silica gel (200 ml) eluting with a mixture of dichloromethane and methanol (9:1 v/v).

- 5 The fractions containing the desired compound were collected and evaporated under reduced pressure to give 4-(3-hydroxypropyloxy)-N-t-butoxycarbonylpiperidine (3.83 g).

NMR (CDCl₃, δ): 1.43 (9H, s), 1.43-1.60 (2H, m),
1.70-1.90 (4H, m), 2.35-2.45 (1H, m), 3.00-3.20
10 (2H, m), 3.35-3.55 (1H, m), 3.60-3.90 (5H, m)

Preparation 139

To a solution of 4-(3-hydroxypropyloxy)-N-t-butyloxycarbonylpiperidine (3.82 g) in ethyl acetate (40 ml)

- 15 were added triethylamine (4.1 ml) and methanesulfonyl chloride (1.37 ml) with stirring under ice-cooling, and the mixture was stirred at the same temperature for 1 hour. To the reaction mixture were added water (50 ml) and ethyl acetate (50 ml) with stirring. The organic layer was
20 separated, washed twice with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate and evaporated in vacuo. The resulting residue was chromatographed on silica gel (150 ml) eluting with a mixture of n-hexane and ethyl acetate (1:1 v/v). The fractions
25 containing the desired compound were collected and evaporated under reduced pressure to give 4-[3-(methanesulfonyloxy)-propyloxy]-N-t-butyloxycarbonylpiperidine (3.77 g).

NMR (CDCl₃, δ): 1.45 (9H, s), 1.45-1.60 (2H, m),
1.70-1.90 (2H, m), 1.90-2.10 (2H, m), 3.01 (3H, s),
30 3.03-3.20 (2H, m), 3.30-3.50 (1H, m), 3.57 (2H, t,
J=5.87Hz), 3.65-3.80 (2H, m), 4.35 (2H, t,
J=6.18Hz)

ESI MASS (m/z)(Positive): 360.3 (M⁺+Na)

Preparation 140

To a solution of 4-[3-(methanesulfonyloxy)propyloxy]-N-t-butyloxycarbonylpiperidine (3.76 g) in methanol (20 ml) was added 28% sodium methoxide methanol solution (22.7 ml), and the mixture was stirred under refluxing for 1.5 hours. The reaction mixture was evaporated in vacuo and dissolved in ethyl acetate (200 ml). The solution was washed twice with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate and evaporated in vacuo. The resulting residue was chromatographed on silica gel (200 ml) eluting with a mixture of n-hexane and ethyl acetate (2:1 v/v). The fractions containing the object compound were collected and evaporated under reduced pressure to give 4-(3-methoxypropyloxy)-N-t-butyloxycarbonylpiperidine (2.66 g).

NMR (CDCl_3 , δ): 1.45 (9H, s), 1.45-1.60 (2H, m), 1.70-1.90 (4H, m), 3.00-3.15 (2H, m), 3.33 (3H, s), 3.35-3.60 (5H, m), 3.65-3.85 (2H, m)

ELSI MASS (m/z): 296.3 ($\text{M}^+ + \text{Na}$)

Preparation 141

A mixture of 1-acetyl-4-(4-hydroxyphenyl)piperazine (5.00 g) in N,N-dimethylformamide (50 ml) was treated with 1,6-dibromohexane (10.5 ml) and potassium carbonate (4.71 g), and the mixture was stirred for 18 hours at ambient temperature. To the reaction mixture was added water (200 ml), and the resulting precipitate was collected by filtration, washed with water and n-hexane successively and dried under reduced pressure to give crude 1-acetyl-4-[4-(6-bromohexyloxy)phenyl]piperazine (10.52 g), that was used in the next reaction directly.

MASS (m/z): 383 ($\text{M}^+ + 1$)

Preparation 142

A solution of crude 1-acetyl-4-[4-(6-bromohexyloxy)phenyl]piperazine (10.52 g) in methanol (105 ml) was treated

- with 28% sodium methoxide in methanol (105 ml), and the solution was refluxed for 7 hours. After cooling, the precipitate was removed by filtration. The filtrate was added to a mixture of methylene chloride and water. The organic layer was taken, dried over magnesium sulfate, filtered and evaporated to give a crude oil. This oil in methylene chloride (20 ml) was treated with acetic anhydride (6.4 ml) under ice-cooling. After 6 hours, the solution was added to a mixture of methylene chloride and water. The organic layer was taken, dried over magnesium sulfate, filtered and evaporated. The residue was purified by silica gel column chromatography eluting with a mixed solvent of methylene chloride-methanol (from 0% to 3% gradient elution) to give 1-acetyl-4-[4-(6-methoxyhexyloxy)phenyl]piperazine (5.38 g) as a pale red solid.
- NMR (DMSO- d_6 , δ): 1.24-1.78 (8H, m), 2.03 (3H, s), 2.86-3.06 (4H, m), 3.21 (3H, s), 3.23-3.36 (2H, m), 3.48-3.65 (4H, m), 3.87 (2H, d, $J=6.4\text{Hz}$), 6.82 (2H, dd, $J=9.2$ and 2.6Hz), 6.88 (2H, dd, $J=9.3$ and 2.6Hz)
- MASS (m/z): 335 (M^++1)

Preparation 143

- A mixture of 1-acetyl-4-[4-(6-methoxyhexyloxy)phenyl]piperazine (4.87 g) and 6N-hydrochloric acid (50 ml) was heated at 75°C for 3 hours. After cooling, the solution was adjusted to pH 11 with 25% sodium hydroxide aqueous solution then the resulting precipitate was collected by filtration, washed with water and dried under reduced pressure to give 4-[4-(6-methoxyhexyloxy)phenyl]piperazine (3.77 g) as a pale brown solid.
- NMR (DMSO- d_6 , δ): 1.25-1.78 (8H, m), 2.74-2.96 (8H, m), 3.21 (3H, s), 3.30 (2H, t, $J=6.3\text{Hz}$), 3.86 (2H, t, $J=6.4\text{Hz}$), 6.79 (2H, d, $J=9.2\text{Hz}$), 6.83 (2H, d, $J=9.5\text{Hz}$)

MASS (m/z): 293 ($M^+ + 1$)

Preparation 144

A mixture of ethyl 4-fluorobenzoate (1.90 g) and 1-[4-(6-methoxyhexyloxy)phenyl]piperazine (3.00 g) in dimethylsulfoxide (45 ml) was treated with potassium carbonate (4.25 g), and the mixture was heated at 150°C for 22 hours. After cooling, water (200 ml) was added to the reaction mixture, and the resulting precipitate was collected by filtration, washed with water and dried under reduced pressure at 50°C for 7 hours to give ethyl 4-[4-(6-methoxyhexyloxy)phenyl]piperazin-1-yl]benzoate (3.20 g) as an other solid.

NMR (DMSO- d_6 , δ): 1.22-1.79 (8H, m), 1.33 (3H, t, J=7.1Hz), 3.08-3.20 (4H, m), 3.21 (3H, s), 3.27-3.40 (2H, m), 3.40-3.54 (4H, m), 3.88 (2H, t, J=6.4Hz), 4.24 (2H, q, J=7.1Hz), 6.83 (2H, d, J=9.0Hz), 6.94 (2H, d, J=9.1Hz), 7.04 (2H, d, J=9.0Hz), 7.81 (2H, d, J=8.9Hz)

MASS (m/z): 441 ($M^+ + 1$)

Preparation 145

A mixture of ethyl 4-[4-[4-(6-methoxyhexyloxy)phenyl]piperazin-1-yl]benzoate (3.00 g) in ethanol (30 ml) was treated with 1N-sodium hydroxide aqueous solution (6.81 ml) then the mixture was refluxed for 24 hours, during which period tetrahydrofuran (20 ml) and 1N-sodium hydroxide aqueous solution (6.81 ml) was added. After cooling, water was added to the mixture, and the acidity of the mixture was adjusted to pH 1 with 1N-hydrochloric acid. The resulting precipitate was filtered, washed with water and dried under reduced pressure to give 4-[4-[4-(6-methoxyhexyloxy)phenyl]piperazin-1-yl]benzoic acid dihydrochloride (2.25g) as an other solid.

NMR (DMSO- d_6 , δ): 1.24-1.78 (8H, m), 3.04-3.21 (4H, m),

3.21 (3H, s), 3.30 (2H, t, J=6.3Hz), 3.34-3.56 (4H, m), 3.88 (2H, t, J=6.4Hz), 6.83 (2H, d, J=9.2Hz), 6.94 (2H, d, J=9.2Hz), 7.01 (2H, d, J=9.0Hz), 7.79 (2H, d, J=8.8Hz)

5 MASS (m/z): 413 ($M^+ + 1$)

Preparation 146

A mixture of 4-[4-[4-(6-methoxyhexyloxy)phenyl]-piperazin-1-yl]benzoic acid dihydrochloride (2.00 g) and 1-hydroxybenzotriazole (0.84 g) in methylene chloride (40 ml) was treated with triethylamine (1.44 ml) and 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride, and the mixture was stirred for 24 hours at ambient temperature. The reaction mixture was added to water. The organic layer was taken, washed with saturated sodium hydrogen carbonate aqueous solution, water and saturated sodium chloride aqueous solution successively, and dried over magnesium sulfate. Magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure. To the residue was added diisopropyl ether, and the resulting precipitate was filtered, washed with diisopropyl ether and dried under reduced pressure to give 4-[4-[4-(6-methoxyhexyloxy)phenyl]-piperazin-1-yl]benzoic acid benzotriazol-1-yl ester (2.30 g) as a dark yellow solid.

25 NMR ($CDCl_3$, δ): 1.33-1.87 (8H, m), 3.15-3.28 (4H, m), 3.34 (3H, s), 3.39 (2H, t, J=6.4Hz), 3.54-3.67 (4H, m), 3.93 (2H, t, J=6.5Hz), 6.87 (2H, d, J=9.3Hz), 6.95 (2H, d, J=9.3Hz), 7.00 (2H, d, J=9.1Hz), 7.37-7.58 (3H, m), 8.10 (1H, d, J=8.2Hz), 8.15 (2H, d, J=9.1Hz)

30 MASS (m/z): 530 ($M^+ + 1$)

Preparation 147

A mixture of 1-acetyl-4-(4-hydroxyphenyl)piperazine (3.00 g) in N,N-dimethylformamide was treated with 3-bromo-1-

propanol (1.60 ml) and potassium carbonate (2.82 g), and the mixture was heated at 60°C for 8 hours. Then 3-bromo-1-propanol (1.60 ml) was added again, and the mixture was heated at 110°C for 6 hours. After cooling, water and methylene chloride were added to the reaction mixture, and the organic layer was taken and dried over magnesium sulfate.

Magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure. The residue was purified by silica gel chromatography eluting with a mixed solvent of methylene chloride-methanol (from 0% to 6% gradient elution) to give 1-acetyl-4-[4-(3-hydroxypropyloxy)phenyl]piperazine (3.53 g) as a pale pink solid.

NMR (DMSO-d₆, δ): 1.82 (2H, t, J=6.3Hz), 2.03 (3H, s), 2.84-3.06 (4H, m), 3.45-3.62 (4H, m), 3.95 (2H, t, J=6.4Hz), 4.13 (2H, t, J=6.5Hz), 4.47-4.60 (1H, m), 6.82 (2H, d, J=9.2Hz), 6.90 (2H, d, J=9.3Hz)

MASS (m/z): 279 (M⁺+1)

Preparation 148

A solution of 1-acetyl-4-[4-(3-hydroxypropyloxy)phenyl]piperazine (3.47 g) in a mixed solvent of tetrahydrofuran (35 ml) and N,N-dimethylformamide (10 ml) was treated with silver(I) oxide (3.18 g) and 3-bromocyclohexene (1.86 ml), and the mixture was stirred at ambient temperature for 16 hours. To the mixture was added silver(I) oxide (3.18 g) and 3-bromocyclohexene (1.86 ml) again, and the mixture was heated at 60°C for 3 hours and then at 110°C for 40 hours. The precipitate was removed by filtration, and the filtrate was evaporated. The residue was purified by silica gel column chromatography eluting with a mixed solvent of methylene chloride-methanol (from 0% to 5% gradient solution) to give crude 1-acetyl-4-[4-[3-(2-cyclohexen-1-yloxy)propyloxy]phenyl]piperazine (1.60 g), that was used in the next reaction directly.

MASS (m/z): 359 (M⁺+1)

Preparation 149

A mixture of crude 1-acetyl-4-[4-[3-(2-cyclohexen-1-yloxy)propyloxy]phenyl]piperazine (1.55 g) in ethanol (16 ml)
5 was hydrogenated at atmospheric pressure with 10% palladium-carbon (0.16 g) for 5 hours. After removal of catalyst by filtration, the filtrate was concentrated in vacuo to give crude 1-acetyl-4-[4-(3-cyclohexyloxypropyloxy)phenyl]piperazine (1.18 g), that was used in the next reaction
10 directly, as a brown oil.

MASS (m/z): 361 ($M^+ + 1$)

The following compound was obtained according to a similar manner to that of Preparation 143.

15

Preparation 150

4-[4-(3-Cyclohexyloxypropyloxy)phenyl]piperazine

NMR ($CDCl_3$, δ): 1.12-1.94 (10H, m), 1.94-2.11 (2H, m),
3.03 (8H, s), 3.57-3.68 (1H, m), 3.86 (2H, t,
20 J=5.9Hz), 4.09 (2H, t, J=5.9Hz), 6.86 (2H, d,
J=9.0Hz), 6.89 (2H, d, J=9.0Hz)

APCI MASS (m/z): 319 ($M^+ + 1$)

The following compound was obtained according to a
25 similar manner to that of Preparation 144.

Preparation 151

Ethyl 4-[4-[4-(3-cyclohexyloxypropyloxy)phenyl]-piperazin-1-yl]benzoate

30 NMR ($CDCl_3$, δ): 1.12-1.95 (10H, m), 1.38 (3H, t, J=7.1Hz), 1.95-2.14 (2H, m), 3.13-3.30 (4H, m), 3.42-3.56 (4H, m), 3.61 (2H, t, J=6.2Hz), 3.81-3.94 (1H, m), 4.10 (2H, t, J=5.9Hz), 4.34 (2H, q, J=7.1Hz), 6.78-7.01 (6H, m), 7.95 (2H, d, J=8.9Hz)

35 MASS (m/z): 467 ($M^+ + 1$)

Preparation 152

A mixture of ethyl 4-[4-[4-(3-cyclohexyloxypropyloxy)-phenyl]piperazin-1-yl]benzoate (290 mg) in the mixed solvent of tetrahydrofuran (15 ml) and ethanol (3 ml) was treated with 10% sodium hydroxide aqueous solution (0.50 ml), and the mixture was refluxed for 8 hours. After cooling, water was added to the reaction mixture, and the acidity of the mixture was adjusted to pH 1 with 1N-hydrochloric acid. The resulting precipitate was filtered, washed with water and dried under reduced pressure to give 4-[4-[4-(3-cyclohexyloxypropyloxy)phenyl]piperazin-1-yl]benzoic acid dihydrochloride (96 mg) as a pale brown solid.

NMR (DMSO- d_6 , δ): 1.08-1.96 (12H, m), 3.07-3.62 (11H, m), 3.95 (2H, t, $J=5.5\text{Hz}$), 6.84 (2H, d, $J=9.1\text{Hz}$), 6.94 (2H, d, $J=9.2\text{Hz}$), 7.03 (2H, d, $J=8.9\text{Hz}$), 7.79 (2H, d, $J=8.7\text{Hz}$)

MASS (m/z): 439 (M^++1)

The following compound was obtained according to a similar manner to that of Preparation 146.

Preparation 153

4-[4-[4-(3-Cyclohexyloxypropyloxy)phenyl]piperazin-1-yl]benzoic acid benzotriazol-1-yl ester

MASS (m/z): 556 (M^++1)

Preparation 154

A solution of 4-bromo-2,6-dimethylphenol (2.00 g) and 1,7-dibromoheptane (5.10 g) in N,N-dimethylformamide (20 ml) was treated with potassium carbonate (2.06 g), and the mixture was stirred for 5 hours at ambient temperature. To the reaction mixture was added water and methylene chloride, and the organic layer was separated and dried over magnesium sulfate. Magnesium sulfate was filtered off, and the

filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography eluting successively with the following solvents: (1) n-hexane, (2) n-hexane:ethyl acetate = 4:1, (3) n-hexane:ethyl acetate = 1:1. The fractions containing the object compound were concentrated in vacuo to give crude 5-bromo-2-(7-bromoheptyloxy)-1,3-dimethylbenzene, that was used in the next reaction directly, as a pale yellow oil.

NMR (CDCl_3 , δ): 1.28-1.98 (10H, m), 2.23 (6H, s),
3.35-3.50 (2H, m), 3.71 (2H, t, $J=6.4\text{Hz}$), 7.13 (2H, s)

Preparation 155

A solution of crude 5-bromo-2-(7-bromoheptyloxy)-1,3-dimethylbenzene (7.81 g) in methanol (78 ml) was treated with 28% sodium methoxide in methanol (78 ml), and the solution was refluxed for 8 hours. After cooling, the reaction mixture was evaporated under reduced pressure, and the residue was extracted with methylene chloride. The organic layer was dried over magnesium sulfate and magnesium sulfate was filtered off, and then the filtrate was evaporated under reduced pressure. The residue was purified by silica gel column chromatography eluting with a mixed solvent of n-hexane-ethyl acetate (from 0% to 7% gradient elution) to give 5-bromo-2-(7-methoxyheptyloxy)-1,3-dimethylbenzene (3.34 g) as a colorless oil.

NMR (CDCl_3 , δ): 1.38-1.69 (8H, m), 1.69-1.89 (2H, m),
2.23 (6H, s), 3.35 (3H, s), 3.28-3.44 (2H, m),
3.65-3.78 (2H, m), 7.13 (2H, s)

MASS (m/z): 329 ($M^+ + 1$)

Preparation 156

To a mixture of cesium carbonate (1.39 g), palladium(II) acetate (34.1 mg) and 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (142 mg) in toluene (3.1 ml) was successively

added ethyl 4-(piperazin-1-yl)benzoate (0.85 g) and a solution of 5-bromo-2-(7-methoxyheptyloxy)-1,3-dimethylbenzene (1.00 g) in toluene (3 ml) in a stream of nitrogen. The mixture was stirred at ambient temperature for 30 minutes and refluxed for a further 20 hours. After cooling, the reaction mixture was concentrated in vacuo and to the residue was added water and methylene chloride. The organic layer was separated, washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography eluting successively with the following solvent: (1) n-hexane, (2) n-hexane:ethyl acetate = 9:1, (3) n-hexane:ethyl acetate = 5:1. The fractions containing the object compound were concentrated in vacuo to give ethyl 4-[4-[4-(7-methoxyheptyloxy)-3,5-dimethylphenyl]piperazin-1-yl]benzoate (0.53 g) as a pale yellow solid.

NMR (CDCl₃, δ): 1.32-1.69 (11H, m), 1.69-1.88 (2H, m), 2.26 (6H, s), 3.17-3.30 (4H, m), 3.33 (3H, s), 3.38 (2H, t, J=6.5Hz), 3.41-3.54 (4H, m), 3.71 (2H, t, J=6.5Hz), 4.34 (2H, q, J=7.1Hz), 6.63 (2H, s), 6.91 (2H, d, J=9.0Hz), 7.95 (2H, d, J=9.0Hz)

MASS (m/z): 483 (M⁺+1)

The following compound was obtained according to a similar manner to that of Preparation 152.

Preparation 157

4-[4-[4-(7-Methoxyheptyloxy)-3,5-dimethylphenyl]-piperazin-1-yl]benzoic acid dihydrochloride

NMR (DMSO-d₆, δ): 1.22-1.60 (8H, m), 1.60-1.79 (2H, m), 2.17 (6H, s), 3.10-3.50 (10H, m), 3.21 (3H, s), 3.64 (2H, t, J=6.3Hz), 6.65 (2H, s), 7.01 (2H, d, J=9.0Hz), 7.79 (2H, d, J=8.8Hz), 12.30 (1H, br s)

MASS (m/z): 455 (M⁺+1)

The following compound was obtained according to a similar manner to that of Preparation 146.

5 Preparation 158

4-[4-[4-(7-Methoxyheptyloxy)-3,5-dimethylphenyl]-piperazin-1-yl]benzoic acid benzotriazol-1-yl ester

NMR (CDCl₃, δ): 1.32-1.89 (10H, m), 2.27 (6H, s),
3.20-3.34 (4H, m), 3.34 (3H, s), 3.38 (2H, t,
10 J=6.5Hz), 3.54-3.68 (4H, m), 3.72 (2H, t, J=6.5Hz),
6.64 (2H, s), 7.00 (2H, d, J=9.1Hz), 7.37-7.62 (3H,
m), 8.09 (2H, d, J=8.3Hz), 8.15 (2H, d, J=9.0Hz)
MASS (m/z): 572 (M⁺+1)

15 The following compound was obtained according to a similar manner to that of Preparation 152.

Preparation 159

20 4-[4-(4-Cyclohexylpiperazin-1-yl)phenyl]benzoic acid dihydrochloride

NMR (DMSO-d₆, δ): 1.03-2.19 (10H, m), 2.80-2.93 (1H, m),
3.10-3.49 (8H, m), 7.08 (2H, d, J=8.4Hz), 7.65 (2H,
d, J=8.6Hz), 7.75 (2H, d, J=8.4Hz), 7.97 (2H, d,
J=8.3Hz)
25 MASS (m/z): 365 (M⁺+1)

The following compound was obtained according to a similar manner to that of Preparation 146.

30 Preparation 160

4-[4-(4-Cyclohexylpiperazin-1-yl)phenyl]benzoic acid benzotriazol-1-yl ester

NMR (CDCl₃, δ): 1.04-1.43 (6H, m), 1.69-2.04 (4H, m),
2.24-2.47 (1H, m), 2.68-2.88 (4H, m), 3.20-3.43
35 (4H, m), 7.03 (2H, d, J=8.8Hz), 7.38-7.66 (3H, m),

7.63 (2H, d, J=8.7Hz), 7.79 (2H, d, J=8.5Hz), 8.12
(1H, d, J=8.2Hz), 8.30 (2H, d, J=8.5Hz)

MASS (m/z): 482 ($M^+ + 1$)

5 Preparation 161

To a solution of methyl 4-(4-hydroxyphenyl)benzoate
(0.94 g), (S)-(-)-2-(tert-butoxycarbonylamino)-3-cyclohexyl-
1-propanol (1.00 g) and triphenylphosphine (1.62 g) in N,N-
dimethylformamide (20 ml) was added dropwise diisopropyl
10 azodicarboxylate (1.21 ml) for 10 minutes under ice-cooling
in a stream of nitrogen. The solution was stirred for 16
hours at ambient temperature, and then water was added to the
reaction mixture, and the mixture was extracted with ethyl
acetate. The organic layer was washed with saturated aqueous
15 sodium chloride solution, dried over magnesium sulfate,
filtered and concentrated in vacuo. The residue was purified
by silica gel column chromatography eluting with a mixed
solvent of n-hexane-ethyl acetate (from 0% to 20% gradient
elution) to give methyl (S)-4-[4-[2-(tert-
20 butoxycarbonylamino)-3-cyclohexylpropyloxy]phenyl]benzoate
(290 mg) as a white solid.

NMR ($CDCl_3$, δ): 1.72-1.93 (13H, m), 1.46 (9H, s),
3.90-4.16 (3H, m), 3.93 (3H, s), 4.63-4.78 (1H, m),
6.93-7.05 (2H, m), 7.50-7.68 (4H, m), 8.06-8.15
25 (2H, m)

MASS (m/z): 368 ($M^+ + 2$ -Boc)

Preparation 162

A solution of methyl (S)-4-[4-[2-(tert-
30 butoxycarbonylamino)-3-cyclohexylpropyloxy]phenyl]benzoate
(0.28 g) in a mixed solvent of methanol (14 ml) and
tetrahydrofuran (3 ml) was treated with 1N-sodium hydroxide
aqueous solution, and the mixture was refluxed for 16 hours.
After cooling, water was added to the mixture, and the
35 acidity of the mixture was adjusted to pH 1 with 1N-

hydrochloric acid. The resulting precipitate was filtered, washed with water and dried under reduced pressure to give (S)-4-[4-[2-(tert-butoxycarbonylamino)-3-cyclohexyl-propyloxy]phenyl]benzoic acid (222 mg) as a white solid.

- 5 NMR (DMSO- d_6 , δ): 0.66-1.48 (8H, m), 1.39 (9H, s),
1.48-1.87 (5H, m), 3.78-3.97 (3H, m), 6.79 (1H, d,
J=7.2Hzs), 7.04 (2H, d, J=8.8Hz), 7.68 (2H, d,
J=8.8Hz), 7.75 (2H, d, J=8.4Hz), 7.98 (2H, d,
J=8.4Hz), 12.83 (1H, br s)
10 MASS (m/z): 354 (M^+ +2-Boc)

The following compound was obtained according to a similar manner to that of Preparation 163.

15 Preparation 163

(S)-4-[4-[2-(tert-Butoxycarbonylamino)-3-cyclohexyl-propyloxy]phenyl]benzoic acid benzotriazol-1-yl ester

- NMR ($CDCl_3$, δ): 0.75-1.96 (13H, m), 1.47 (9H, s),
3.92-4.20 (3H, m), 4.60-4.79 (1H, m), 7.04 (2H, d,
20 J=8.8Hz), 7.40-7.63 (3H, m), 7.64 (2H, d, J=8.7Hz),
7.79 (2H, d, J=8.4Hz), 8.12 (1H, d, J=8.1Hz), 8.32
(2H, d, J=8.4Hz)
MASS (m/z): 571 (M^+ +1)

25 Preparation 164

A mixture of 1-fluoro-4-nitrobenzene (2.71 ml), 1,2,3,6-tetrahydro-4-phenylpyridine hydrochloride (5 g) and potassium carbonate (8.83 g) in dimethylsulfoxide (50 ml) was stirred for 1 hour at 100°C. The reaction mixture was pulverized
30 with water. The precipitate was collected by filtration, and dried under reduced pressure to give 4-(4-phenyl-3,6-dihydro-2H-pyridin-1-yl)nitrobenzene.

IR (KBr): 1589.1, 1311.4, 1108.9 cm^{-1}

- NMR ($CDCl_3$, δ): 2.73-2.77 (2H, m), 3.73 (2H, t,
35 J=11.3Hz), 4.09 (2H, dd, J=2.5 and 5.9Hz), 6.16-

6.20 (1H, m), 6.80-6.88 (2H, m), 7.29-7.45 (5H, m),
8.12-8.20 (2H, m)

MASS (m/z): 281 ($M^+ + 1$)

5 Preparation 165

To a solution of 4-(4-phenyl-3,6-dihydro-2H-pyridin-1-yl)nitrobenzene (6.4 g) in ethyl alcohol (192 ml) and tetrahydrofuran (192 ml) was added 10% palladium on carbon (0.64 g), and hydrogen gas at atmosphere pressure for 6
10 hours. The reaction mixture was filtered through celite and evaporated under reduced pressure to give 1-(4-aminophenyl)-4-phenylpiperidine (5.66 g).

IR (KBr): 1604.5, 1511.9, 1382.7, 1207.2 cm^{-1}

NMR (CDCl_3 , δ): 1.84-1.97 (4H, m), 2.52-2.78 (3H, m),
15 3.10-3.73 (4H, m), 6.63-6.70 (2H, m), 6.84-6.92
(2H, m), 7.17-7.37 (5H, m)

MASS (m/z): 253 ($M^+ + 1$)

Preparation 166

20 To a solution of 1-(4-aminophenyl)-4-phenylpiperidine (2 g) in 47% hydrobromic acid (20 ml) and acetic acid (23 ml) was added dropwise sodium nitrite (0.55 g) in water (1 ml) under ice-cooling. The solution was then stirred for 30 minutes at 0°C. The reaction mixture was added dropwise
25 copper(I) bromide (2.27 g) in 47% hydrobromic acid (2.3 ml) under ice-cooling. The reaction mixture was then stirred for 1.5 hours at ambient temperature. The reaction mixture was pulverized with water. The precipitate was collected by filtration. The powder was added 1N-sodium hydroxide (21 ml)
30 and extracted with ethyl acetate. The organic layer was separated, washed with brine, dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography over silica using dichloromethane/n-
35 hexane (1:1) as the elution to give 1-(4-bromophenyl)-4-

phenylpiperidine (1.23 g).

IR (KBr): 1583.3, 1488.8, 1382.7, 1214.9 cm^{-1}

NMR (CDCl_3 , δ): 1.77-1.96 (4H, m), 2.57-2.71 (1H, m),
2.74-2.88 (2H, m), 3.73-3.79 (2H, m), 6.81-6.89
5 (2H, m), 7.18-7.38 (7H, m)

MASS (m/z): 316 ($\text{M}^+ + 1$)

Preparation 167

A mixture of piperazine-1-carboxylic acid tert-butyl
10 ester (2.02 g), 1-(4-bromophenyl)-4-phenylpiperidine (2.86
g), tris(dibenzylidene acetone)(chloroform)-di-palladium(0)
(0.19 g), (S)-(-)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
(0.28 g) and sodium tert-butoxide (1.74 g) in toluene (29 ml)
was stirred for 6 hours at 90°C. The reaction mixture was
15 added to a mixture of water and ethyl acetate. The organic
layer was taken and dried over magnesium sulfate. The
magnesium sulfate was filtered off, and the filtrate was
evaporated under reduced pressure. The residue was purified
by column chromatography over silica using
20 dichloromethane/methyl alcohol (50:1) as the elution to give
4-[4-(4-phenylpiperidin-1-yl)phenyl]piperazine-1-carboxylic
acid tert-butyl ester (2.93 g).

IR (KBr): 1691.3, 1596.8, 1116.6 cm^{-1}

NMR (CDCl_3 , δ): 1.48 (9H, s), 1.87-1.99 (4H, m),
25 2.60-2.90 (3H, m) 3.00-3.16 (4H, m), 3.55-3.71 (6H,
m), 6.87-6.99 (4H, m), 7.21-7.53 (5H, m)

MASS (m/z): 422 ($\text{M}^+ + 1$)

Preparation 168

To a solution of 4-[4-(4-phenylpiperidin-1-
30 yl)phenyl]piperazine-1-carboxylic acid tert-butyl ester (2.45
g) in 1,4-dioxane (62 ml) was added dropwise 4N-HCl/1,4-
dioxane (58 ml) at ambient temperature. The reaction mixture
was stirred for 110 minutes at ambient temperature, and
35 stirred for 2 hours at 80°C. The precipitate was filtered

and dried to give 1-[4-(4-phenylpiperidin-1-yl)phenyl]-piperazine trihydrochloride salt (2.07 g).

IR (KBr): 3494.4, 3237.9, 1635.3, 1498.4 cm^{-1}

NMR (DMSO-d_6 , δ): 1.98-3.90 (18H, m), 7.02-7.41 (7H, m),
5 7.82-7.86 (2H, m)

MASS (m/z): 322.4 ($M^+ + 1$) (free)

Preparation 169

A mixture of 4-[4-(4-phenylpiperidin-1-yl)phenyl]piperazine trihydrochloride salt (1.77 g) and 1N-sodium hydroxide (62 ml) in dichloromethane (62 ml) was stirred for 30 minutes at ambient temperature. The organic layer was separated, washed with brine, dried over magnesium sulfate. The magnesium sulfate was filtered off, and the
15 filtrate was evaporated under reduced pressure to give 1-[4-(4-phenylpiperidin-1-yl)phenyl]piperazine (1.19 g).

Preparation 170

A mixture of 4-fluorobenzoic acid ethyl ester (1.25 g),
20 1-[4-(4-phenylpiperidin-1-yl)phenyl]piperazine (1.19 g) and potassium carbonate (1.53 g) in dimethylsulfoxide (18 ml) was stirred for 12 hours at 150°C. The reaction mixture was pulverized with water. The mixture was extracted with dichloromethane. The organic layer was separated, washed
25 with brine, dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography over silica using dichloromethane/methyl alcohol (200:1) as the elution. The powder was recrystallized
30 from toluene (60 ml). The crystal was collected by filtration, and dried under reduced pressure to give 4-[4-[4-(4-phenylpiperidin-1-yl)phenyl]piperazin-1-yl]benzoic acid ethyl ester (0.80 g).

IR (KBr): 1702.8, 1513.8, 1232.3 cm^{-1}

35 NMR (CDCl_3 , δ): 1.37 (3H, t, $J=7.1\text{Hz}$), 1.89-2.00 (4H,

m), 2.55-2.84 (3H, m), 3.22-3.27 (4H, m), 3.46-3.51 (4H, m), 3.66-3.72 (2H, m), 4.34 (2H, q, J=7.1Hz), 6.90-7.03 (6H, m), 7.18-7.37 (5H, m), 7.93-7.98 (2H, m)

5 MASS (m/z): 470

Preparation 171

To a mixture of 4-[4-[4-(4-phenylpiperidin-1-yl)phenyl]piperazin-1-yl]benzoic acid ethyl ester (0.78 g) in ethyl alcohol (39 ml) and 1,4-dioxane (39 ml) was added 10% NaOH aq. (1.3 ml) and refluxed for 16 hours. The reaction mixture was adjusted to pH 1-2 with 1N-HCl and the resulting precipitate was collected by filtration, and dried under reduced pressure to give 4-[4-[4-(4-phenylpiperidin-1-yl)phenyl]piperazin-1-yl]benzoic acid dihydrochloride salt (0.65 g).

IR (KBr): 2840.6, 1670.1, 1602.6, 1232.3 cm^{-1}

NMR ($\text{CDCl}_3 + \text{CD}_3\text{OD}$, δ): 2.05-2.20 (2H, m), 2.70-3.10 (3H, m), 3.40-3.85 (12H, m), 6.91-7.06 (4H, m), 7.25-7.37 (7H, m), 7.95-7.99 (2H, m)

MASS (m/z): 442 (free)

Preparation 172

To a suspension of 4-[4-[4-(4-phenylpiperidin-1-yl)phenyl]piperazin-1-yl]benzoic acid dihydrochloride salt (0.62 g) and 1-hydroxybenzotriazole (0.2 g) in dichloromethane (12 ml) was added 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide (0.22 g) and stirred for 22 hours at ambient temperature. The reaction mixture was added to a mixture of water and dichloromethane. The organic layer was taken and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure to give 4-[4-[4-(4-phenylpiperidin-1-yl)phenyl]piperazin-1-yl]benzoic acid benzotriazol-1-yl ester (0.41 g).

IR (KBr): 1780.0, 1600.6, 1513.8, 1230.4 cm^{-1}

NMR (CDCl_3 , δ): 1.85-2.05 (4H, m), 2.60-2.90 (3H, m),
3.25-3.80 (10H, m), 6.95-7.55 (15H, m), 8.08-8.18
(2H, m)

5 MASS (m/z): 559 ($\text{M}^+ + 1$)

Preparation 173

To a suspension of 4-hydroxy-4-phenylpiperidine (5 g)
and triethylamine (4.32 ml) in dichloromethane (50 ml) was
10 added dropwise di-tert-butylidicarbonate (6.16 g) in
dichloromethane (6 ml) under ice-cooling. The reaction
mixture was then stirred for 4 hours at ambient temperature.
The reaction mixture was pulverized with water. The organic
layer was separated, washed with brine, dried over magnesium
15 sulfate. The magnesium sulfate was filtered off, and the
filtrate was evaporated under reduced pressure. The residue
was purified by column chromatography over silica using
dichloromethane/methyl alcohol (30:1) as the elution to give
4-hydroxy-4-phenylpiperidine-1-carboxylic acid tert-butyl
20 ester (7.2 g).

IR (KBr): 3463.5, 1675.8, 1664.3, 1170.6 cm^{-1}

NMR (CDCl_3 , δ): 1.48 (9H, s), 1.63-2.08 (5H, m),
3.19-3.30 (2H, m), 3.90-4.10 (2H, m), 7.27-7.50
(5H, m)

25 MASS (m/z): 178 ($\text{M}^+ - \text{Boc} + 1$)

Preparation 174

To a solution of 4-hydroxy-4-phenylpiperidine-1-
carboxylic acid tert-butyl ester (7.1 g) in N,N-
30 dimethylformamide (71 ml) was added 60% sodium hydride in
mineral oil (1.13 g) under ice-cooling, and stirred for 1
hour at ambient temperature. The suspension was then stirred
for 1.5 hours at 60°C. To the reaction mixture was added
iodomethane (32 ml) at 40°C, and stirred for 30 minutes at
35 45°C. Water and ethyl acetate were added with stirring, and

the organic layer was separated, washed with brine, dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography over silica
5 using n-hexane/ethyl acetate (4:1) as the elution to give 4-methoxy-4-phenylpiperidine-1-carboxylic acid tert-butyl ester (6.63 g).

IR (KBr): 1700.9, 1685.5, 1170.6 cm^{-1}

NMR (CDCl_3 , δ): 1.47 (9H, s), 1.79-2.05 (4H, m), 2.98
10 (3H, s), 3.12-3.24 (2H, m), 3.90-4.10 (2H, m),
7.28-7.39 (5H, m)

MASS (m/z): 192 ($\text{M}^+ - \text{Boc} + 1$)

Preparation 175

15 To a solution of 4-methoxy-4-phenylpiperidine-1-carboxylic acid tert-butyl ester (6.5 g) in ethyl acetate (65 ml) was added dropwise 4N-HCl/ethyl acetate (56 ml) at ambient temperature. The reaction mixture was stirred for 1.5 hours at ambient temperature. To the reaction mixture
20 was added diisopropyl ether. The precipitate was collected by filtration to give powder. The powder was adjusted to pH 11 with 1N-NaOH, and extracted with ethyl acetate. The organic layer was separated, washed with brine, dried over magnesium sulfate. The magnesium sulfate was filtered off,
25 and the filtrate was evaporated under reduced pressure to give 4-methoxy-4-phenylpiperidine (3.47 g).

IR (KBr): 3322.7, 1535.1, 1070.3 cm^{-1}

NMR (CDCl_3 , δ): 1.80-2.07 (5H, m), 2.88-3.15 (7H, m),
7.28-7.44 (5H, m)

30 MASS (m/z): 192 ($\text{M}^+ + 1$)

Preparation 176

A mixture of 1-acetyl-4-(4-trifluoromethanesulfonyloxyphenyl)piperazine (3 g), 4-methoxy-4-phenylpiperidine (1.63 g), acetic acid palladium(II) salt
35

(0.11 g), racemic-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.42 g) and cesium carbonate (3.88g) in toluene (17 ml) was stirred for 30 minutes at ambient temperature. After being stirred for a further 17 hours at 100°C, the reaction mixture was diluted with dichloromethane. The suspension was filtered through celite, and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography over silica using ethyl acetate/methyl alcohol (30:1) as the elution to give 1-acetyl-4-[4-(4-methoxy-4-phenylpiperidin-1-yl)phenyl]piperazine (2.65 g).

IR (KBr): 1643.1, 1321.0, 1074.2 cm^{-1}

NMR (CDCl_3 , δ): 2.14 (3H, s), 2.14-2.17 (4H, m), 2.98 (3H, s), 2.98-3.45 (8H, m), 3.59-3.79 (4H, m), 6.92-7.00 (4H, m), 7.28-7.47 (5H, m)

MASS (m/z): 394 ($\text{M}^+ + 1$)

Preparation 177

A mixture of 1-acetyl-4-[4-(4-methoxy-4-phenylpiperidin-1-yl)phenyl]piperazine (2.5 g) and 10% NaOH aq. (10.2 ml) in ethyl alcohol (50 ml) was refluxed for 23.5 hours. The reaction mixture was evaporated under reduced pressure. The residue was washed with water, and dried to give 1-[4-(4-methoxy-4-phenylpiperidin-1-yl)phenyl]piperazine (2.18 g).

IR (KBr): 3290.0, 1513.8, 1232.3, 1074.2 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ): 1.91-2.11 (4H, m), 2.80-3.17 (11H, m), 3.20-3.45 (5H, m), 6.79-6.91 (4H, m), 7.25-7.46 (5H, m)

MASS (m/z): 352 ($\text{M}^+ + 1$)

The following compound was obtained according to a similar manner to that of Preparation 170.

Preparation 178

4-[4-[4-(4-Methoxy-4-phenylpiperidin-1-yl)phenyl]piperazin-1-yl]benzoic acid ethyl ester

IR (KBr): 1702.8, 1511.9, 1236.1, 1105.0 cm^{-1}
NMR (CDCl_3 , δ): 1.37 (3H, t, $J=7.1\text{Hz}$), 2.14-2.18 (4H, m), 3.01 (3H, s), 3.06-3.50 (12H, m), 4.34 (2H, q, $J=7.1\text{Hz}$), 6.90-7.03 (6H, m), 7.28-7.47 (5H, m), 7.93-7.98 (2H, m)
MASS (m/z): 500 (M^++1)

The following compound was obtained according to a similar manner to that of Preparation 170.

Preparation 179

4-[4-[4-(4-Methoxy-4-phenylpiperidin-1-yl)phenyl]piperazin-1-yl]benzoic acid dihydrochloride
IR (KBr): 2960.2, 1702.8, 1604.5, 1184.1 cm^{-1}
NMR ($\text{DMSO}-d_6$, δ): 2.20-3.70 (19H, m), 7.02-7.62 (11H, m), 7.78-7.83 (2H, m)
MASS (m/z): 472 (M^++1) (free)

The following compound was obtained according to a similar manner to that of Preparation 172.

Preparation 180

4-[4-[4-(4-Methoxy-4-phenylpiperidin-1-yl)phenyl]piperazin-1-yl]benzoic acid benzotriazol-1-yl ester
IR (KBr): 1762.6, 1600.6, 1230.4, 1184.1 cm^{-1}
NMR (CDCl_3 , δ): 2.10-2.20 (4H, m), 3.01 (3H, s), 3.05-3.64 (12H, m), 6.98-7.04 (6H, m), 7.32-7.51 (8H, m), 8.07-8.17 (3H, m)
MASS (m/z): 589 (M^++1)

The following compound was obtained according to a similar manner to that of Preparation 176.

Preparation 181

1-[4-[4-(1,4-Dioxo-8-azaspiro[4.5]decan-8-yl)phenyl]-

piperazin-1-yl]ethanone

IR (KBr): 1648.8, 1637.3, 1334.5, 1230.4, 1099.2 cm^{-1} NMR (DMSO- d_6 , δ): 1.67-1.73 (4H, m), 2.03 (3H, s),
2.90-3.14 (8H, m), 3.50-3.60 (4H, m), 3.90 (4H, s),
6.86 (4H, s)MASS (m/z): 346 (M^+ +1)

The following compound was obtained according to a
similar manner to that of Preparation 177.

Preparation 182

8-(4-Piperazinylphenyl)-1,4-dioxo-8-azaspiro[4.5]decane

IR (KBr): 3284.2, 1513.8, 1328.7, 1110.8 cm^{-1} NMR (DMSO- d_6 , δ): 1.70 (4H, t, $J=5.7\text{Hz}$), 2.79-2.91 (8H,
m), 3.06-3.12 (4H, m), 3.25-3.38 (5H, m), 6.77-6.88
(4H, m)MASS (m/z): 304 (M^+ +1)

The following compound was obtained according to a
similar manner to that of Preparation 170.

Preparation 1834-[4-(1,4-Dioxo-8-azaspiro[4.5]decan-8-
yl)phenyl]piperazin-1-yl]benzoic acid ethyl esterIR (KBr): 1704.8, 1511.9, 1224.6, 1108.9 cm^{-1} NMR (CDCl_3 , δ): 1.37 (3H, t, $J=7.1\text{Hz}$), 1.86 (4H, t,
 $J=5.7\text{Hz}$), 3.20-3.25 (8H, m), 3.45-3.50 (4H, m),
3.99 (4H, s), 4.34 (2H, q, $J=7.1\text{Hz}$), 6.89-6.93 (6H,
m), 7.91-7.97 (2H, m)MASS (m/z): 452 (M^+ +1)

The following compound was obtained according to a
similar manner to that of Preparation 171.

Preparation 184

4-[4-[4-(1,4-Dioxo-8-azaspiro[4.5]decan-8-yl)phenyl]piperazin-1-yl]benzoic acid dihydrochloride

IR (KBr): 2962.1, 1670.1, 1321.0, 1230.4 cm^{-1}

5 NMR (DMSO- d_6 , δ): 1.70-2.00 (4H, m), 3.10-3.70 (16H, m),
7.00-7.20 (6H, m), 7.78-7.82 (2H, m)

MASS (m/z): 424 ($M^+ + 1$) (free)

The following compound was obtained according to a
10 similar manner to that of Preparation 172.

Preparation 185

4-[4-[4-(1,4-Dioxo-8-azaspiro[4.5]decan-8-yl)phenyl]-piperazin-1-yl]benzoic acid benzotriazol-1-yl ester

15 IR (KBr): 1781.9, 1600.6, 1232.3 cm^{-1}

NMR (CDCl_3 , δ): 1.86 (4H, t, $J=5.7\text{Hz}$), 3.21-3.28 (8H, m),
3.59-3.64 (4H, m), 4.00 (4H, s), 6.95-7.02 (6H, m),
7.40-7.58 (3H, m), 8.07-8.17 (3H, s)

MASS (m/z): 541 ($M^+ + 1$)

20 The following compound was obtained according to a
similar manner to that of Preparation 176.

Preparation 186

25 1-Acetyl-4-[4-(4-cyclohexyloxypiperidin-1-yl)phenyl]-piperazine

IR (KBr): 1621.8, 1236.1, 1101.2 cm^{-1}

NMR (CDCl_3 , δ): 1.20-2.00 (14H, m), 2.13 (3H, s),

2.75-3.78 (14H, m), 6.78-7.83 (4H, m)

30 MASS (m/z): 386 ($M^+ + 1$)

Preparation 187

A mixture of 1-acetyl-4-[4-(4-cyclohexyloxypiperidin-1-yl)phenyl]piperazine (0.37 g) and 10% sodium hydroxide (1.9
35 ml) in ethyl alcohol (7.4 ml) was refluxed for 10 hours. The

reaction mixture was evaporated under reduced pressure. The residue was washed with water, and dried to give 1-[4-(4-cyclohexyloxypiperidin-1-yl)phenyl]piperazine (0.32 g).

- 5 The following compound was obtained according to a similar manner to that of Preparation 170.

Preparation 188

- 10 4-[4-[4-(4-Cyclohexyloxypiperidin-1-yl)phenyl]piperazin-1-yl]benzoic acid ethyl ester

IR (KBr): 1706.7, 1234.2, 1110.8 cm^{-1}

NMR (CDCl_3 , δ): 1.23-1.91 (17H, m), 2.77-2.86 (2H, m),
3.19-3.24 (4H, m), 3.30-3.60 (8H, m), 4.34 (2H, q,
J=7.1Hz), 6.89-6.93 (6H, m), 7.93-7.97 (2H, m)

- 15 MASS (m/z): 492 ($\text{M}^+ + 1$)

The following compound was obtained according to a similar manner to that of Preparation 171.

- 20 Preparation 189

4-[4-[4-(4-Cyclohexyloxypiperidin-1-yl)phenyl]piperazin-1-yl]benzoic acid dihydrochloride

IR (KBr): 1672.0, 1322.9, 1230.4 cm^{-1}

- 25 NMR ($\text{DMSO}-d_6$, δ): 1.00-2.20 (14H, m), 3.20-4.00 (14H, m), 6.80-8.00 (8H, m)

MASS (m/z): 464 ($\text{M}^+ + 1$) (free)

The following compound was obtained according to a similar manner to that of Preparation 172.

30

Preparation 190

4-[4-[4-(4-Cyclohexyloxypiperidin-1-yl)phenyl]piperazin-1-yl]benzoic acid benzotriazol-1-yl ester

IR (KBr): 1781.9, 1600.6, 1513.8, 1230.4 cm^{-1}

- 35 NMR (CDCl_3 , δ): 1.13-2.10 (14H, m), 2.80-2.88 (2H, m),

3.22-3.64 (12H, m), 6.94-7.02 (6H, m), 7.39-7.58
(3H, m), 8.07-8.17 (3H, m)

MASS (m/z): 581 ($M^+ + 1$)

5 Preparation 191

To a suspension of 1-(4-hydroxyphenyl)piperazine (50 g) and potassium carbonate (46.5 g) in N,N-dimethylformamide (100 ml) was added dropwise benzyl chloroformate (47.86 g) at 0 to 10°C, and stirred for 4 hours at ambient temperature.

- 10 The reaction mixture was poured into water, and extracted with ethyl acetate. The organic layer was washed with brine and dried, and the solvent was evaporated under reduced pressure. The residue was chromatographed on a column of silica gel eluting with dichloromethane/methyl alcohol (30:1)
- 15 to give 4-(4-hydroxyphenyl)piperazine-1-carboxylic acid benzyl ester (60.8 g).

IR (KBr): 3336.2, 1658.5, 1226.5 cm^{-1}

NMR (CDCl_3 , δ): 3.00 (4H, t, $J=4.9\text{Hz}$), 3.66 (4H, t, $J=5.1\text{Hz}$), 5.16 (2H, s), 5.29 (1H, s), 6.74-6.86
20 (4H, m), 7.30-7.40 (5H, m)

MASS (m/z): 313 ($M^+ + 1$)

Preparation 192

To a solution of 4-(4-hydroxyphenyl)piperazine-1-carboxylic acid benzyl ester (22.38 g) and pyridine (8.7 ml) in dichloromethane (336 ml) was added dropwise trifluoromethanesulfonic anhydride (15.7 ml) at 0 to 10°C, and stirred for 2 hours. The reaction mixture was washed successively with 0.5N hydrochloric acid, saturated sodium
30 hydrogen carbonate, water, brine, dried, and evaporated under reduced pressure. The residue was chromatographed on a column of silica gel eluting with dichloromethane/methyl alcohol (50:1) to give 4-(4-trifluoromethanesulfonyloxyphenyl)piperazine-1-carboxylic acid benzyl ester (21.06 g).

- 35 IR (KBr): 1685.5, 1511.9, 1427.1 cm^{-1}

NMR (CDCl₃, δ): 3.17 (4H, t, J=5.0Hz), 3.67 (4H, t, J=5.2Hz), 5.16 (2H, s), 6.87-7.18 (4H, m), 7.34-7.38 (5H, m)
MASS (m/z): 445 (M⁺+1)

5

The following compound was obtained according to a similar manner to that of Preparation 176.

Preparation 193

10 4-[4-(1,4-Dioxa-8-azaspiro[4.5]decan-8-yl)phenyl]-piperazine-1-carboxylic acid benzyl ester
IR (KBr): 1697.1, 1519.6, 1230.4 cm⁻¹
NMR (CDCl₃, δ): 1.85 (4H, t, J=5.7Hz), 3.00-3.05 (4H, m), 3.21 (4H, t, J=5.7Hz), 3.65 (4H, t, J=5.1Hz),
15 3.99 (4H, s), 5.16 (2H, s), 6.84-6.95 (4H, m), 7.36-7.39 (5H, m)
MASS (m/z): 438 (M⁺+1)

Preparation 194

20 To a solution of 4-[4-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)phenyl]piperazine-1-carboxylic acid benzyl ester (30 g) in 1,4-dioxane (450 ml) was added 1N-hydrochloric acid (240 ml) at ambient temperature, and the mixture was stirred for 7 hours at 90°C. The reaction mixture was poured into water.
25 The mixture was adjusted to pH 10-12 with 1N-sodium hydroxide (480 ml), and extracted with ethyl acetate. The organic layer was washed with water, brine, and dried, and evaporated under reduced pressure. The residue was chromatographed on a column of silica gel eluting with dichloromethane/methyl
30 alcohol (50:1) to give 4-[4-(4-oxopiperidin-1-yl)phenyl]piperazine-1-carboxylic acid benzyl ester (21.22 g).

IR (KBr): 1718.3, 1683.6, 1232.3 cm⁻¹
NMR (CDCl₃, δ): 2.55 (4H, t, J=6.0Hz), 3.05 (4H, t, J=4.8Hz), 3.49 (4H, t, J=6.0Hz), 3.66 (4H, t,

35

J=5.1Hz)

MASS (m/z): 394 ($M^+ + 1$)

Preparation 195

5 To a suspension of 4-(4-chlorophenyl)-4-hydroxypiperidine (8 g) and triethylamine (5.8 ml) in dichloromethane (80 ml) was added di-tert-butylidicarbonate (9.07 g) under ice-cooling. The suspension was then stirred for 5 hours at ambient temperature. The reaction mixture was
10 evaporated under reduced pressure. The residue was diluted with ethyl acetate and washed with water, washed with brine, and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography
15 over silica using n-hexane/ethyl acetate (3:1) as the elution to give 4-(4-chlorophenyl)-4-hydroxypiperidine-1-carboxylic acid tert-butyl ester (11.76 g).

IR (KBr): 3461.6, 1675.8, 1662.3, 1166.7 cm^{-1}

20 NMR (CDCl_3 , δ): 1.48 (9H, s), 1.62-2.04 (5H, m),
3.16-3.28 (2H, m), 3.97-4.09 (2H, m), 7.30-7.44 (4H, m)

MASS (m/z): 212 ($M^+ - \text{Boc}$)

The following compound was obtained according to a
25 similar manner to that of Preparation 174.

Preparation 196

4-(4-Chlorophenyl)-4-methoxypiperidine-1-carboxylic acid
tert-butyl ester

30 IR (KBr): 1695.1, 1423.2, 1170.6 cm^{-1}

NMR (CDCl_3 , δ): 1.47 (9H, s), 1.72-2.04 (4H, m), 2.97 (3H, s), 3.07-3.22 (2H, m), 3.90-4.04 (2H, m),
7.27-7.37 (4H, m)

MASS (m/z): 348.1 ($M^+ + \text{Na}$)

35

The following compound was obtained according to a similar manner to that of Preparation 175.

Preparation 197

5 4-(4-Chlorophenyl)-4-methoxypiperidine
IR (Film): 3305.4, 1490.7, 1135.9, 1072.2 cm⁻¹
NMR (CDCl₃, δ): 1.75-2.03 (4H, m), 2.86-3.11 (8H, m),
 7.33 (4H, s)
MASS (m/z): 226.2

The following compound was obtained according to a similar manner to that of Preparation 164.

Preparation 198

15 1-(4-Nitrophenyl)-4-(4-chlorophenyl)-4-methoxypiperidine
IR (KBr): 1594.8, 1319.1, 1066.4 cm^{-1}
NMR (CDCl_3 , δ): 1.91-2.20 (4H, m), 3.02 (3H, s), 3.34-
3.48 (2H, m), 3.79-3.86 (2H, m), 6.83-6.91 (2H, m),
7.29-7.39 (4H, m), 8.09-8.17 (2H, m)
20 MASS (m/z): 347.2

Preparation 199

A mixture of 1-(4-nitrophenyl)-4-(4-chlorophenyl)-4-methoxypiperidine (8.9 g), iron powder (10.7 g) and ammonium chloride (1.07 g) in ethanol (445 ml) and water (44.5 ml) was stirred at reflux for 5.5 hours. The insoluble material was filtered off, and the filtrate was evaporated under reduced pressure. To the residue was added a mixture of ethyl acetate (150 ml), water (100 ml) and saturated sodium hydrogen carbonate (50 ml). The organic layer was separated, washed with brine, dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure. To the residue was added a mixture of diisopropyl ether (10 ml) and n-hexane (20 ml). The precipitate was collected by filtration, and dried under

reduced pressure to give 1-(4-aminophenyl)-4-(4-chlorophenyl)-4-methoxypiperidine (7.3 g).

IR (KBr): 3342.0, 1614.1, 1517.7, 1066.4 cm^{-1}

NMR (CDCl_3 , δ): 2.04-2.20 (4H, m), 2.99 (3H, s),
3.03-3.34 (6H, m), 6.64-6.70 (4H, m), 7.30-7.45
(4H, m)

MASS (m/z): 317.3

The following compound was obtained according to a
similar manner to that of Preparation 166.

Preparation 200

1-(4-Bromophenyl)-4-(4-chlorophenyl)-4-methoxypiperidine

IR (KBr): 1589.1, 1494.6, 1249.6, 1062.6 cm^{-1}

NMR (CDCl_3 , δ): 1.96-2.15 (4H, m), 2.99 (3H, s), 3.08-
3.22 (2H, m), 3.40-3.55 (2H, m), 6.81-6.87 (2H, m),
7.30-7.38 (6H, m)

MASS (m/z): 382 ($\text{M}^+ + 1$)

The following compound was obtained according to a
similar manner to that of Preparation 167.

Preparation 201

4-[4-[4-(4-Chlorophenyl)-4-methoxypiperidin-1-yl]phenyl]piperazine-1-carboxylic acid tert-butyl ester

IR (KBr): 1695.1, 1511.9, 1234.2 cm^{-1}

NMR (CDCl_3 , δ): 1.48 (9H, s), 2.05-2.15 (4H, m), 2.99
(3H, s), 3.00-3.16 (6H, m), 3.37-3.43 (2H, m),
3.55-3.60 (4H, m), 6.87-6.99 (4H, m), 7.35 (4H, s)

MASS (m/z): 486 ($\text{M}^+ + 1$)

Preparation 202

To a solution of 4-[4-[4-(4-chlorophenyl)-4-methoxypiperidin-1-yl]phenyl]piperazine-1-carboxylic acid
tert-butyl ester (1.56 g) in ethyl acetate (62 ml) was added

dropwise 4N-HCl/ethyl acetate (40 ml) at ambient temperature.

The reaction mixture was stirred for 33 hours at ambient temperature. The precipitate was collected by filtration, and dried under reduced pressure to give 4-[4-[4-(4-chlorophenyl)-4-methoxypiperidin-1-yl]phenyl]-piperazine trihydrochloride salt (1.52 g).

IR (KBr): 3382.5, 1504.2, 1255.4 cm^{-1}

NMR (DMSO_6 , δ): 2.24-3.76 (20H, m), 7.12-7.84 (8H, m)

MASS (m/z): 386 (free)

The following compound was obtained according to a similar manner to that of Preparation 169.

Preparation 203

4-[4-[4-(4-Chlorophenyl)-4-methoxypiperidin-1-yl]phenyl]piperazine

The following compound was obtained according to a similar manner to that of Preparation 170.

Preparation 204

4-[4-[4-(4-Chlorophenyl)-4-methoxypiperidin-1-yl]phenyl]piperazin-1-yl]benzoic acid ethyl ester

IR (KBr): 1702.8, 1602.6, 1513.8, 1234.2 cm^{-1}

MASS (m/z): 534 ($\text{M}^+ + 1$)

The following compound was obtained according to a similar manner to that of Preparation 171.

Preparation 205

4-[4-[4-(4-Chlorophenyl)-4-methoxypiperidin-1-yl]phenyl]piperazin-1-yl]benzoic acid dihydrochloride

IR (KBr): 2962.1, 1697.1, 1602.6, 1515.8, 1224.6 cm^{-1}

MASS (m/z): 506 ($\text{M}^+ + 1$) (free)

The following compound was obtained according to a similar manner to that of Preparation 172.

Preparation 206

- 5 4-[4-[4-[4-(4-Chlorophenyl)-4-methoxypiperidin-1-yl]phenyl]piperazin-1-yl]benzoic acid benzotriazol-1-yl ester
IR (KBr): 1772.3, 1762.6, 1598.7, 1230.4, 1184.1 cm^{-1}
NMR ($\text{CDCl}_3 + \text{CD}_3\text{OD}$, δ): 2.11-2.17 (3H, m), 3.01 (3H, s),
3.05-3.66 (12H, m), 6.95-7.04 (6H, m), 7.37-7.60
10 (7H, m), 8.07-8.17 (3H, m)
MASS (m/z): 623 ($\text{M}^+ + 1$)

Preparation 207

- 60% Sodium hydride (1.01 g) was added slowly to a
15 suspension of 4,4'-bicyclohexanol (5 g) in N,N-dimethylformamide (50 ml) at ambient temperature, and the mixture was stirred for 6 hours at 80°C. To the mixture was added dropwise n-propylbromide (2.29 ml) at 0-5°C, and the reaction mixture was stirred for 18.5 hours at 80°C. The
20 reaction mixture was poured into water, and extracted with ethyl acetate. The organic layer was washed with brine and dried, and the solvent was evaporated under reduced pressure.
The residue was chromatographed on a column of silica gel eluting with dichloromethane/methyl alcohol (50:1) to give
25 4'-propyl-4-hydroxy-1,1'-bicyclohexane (1.21 g).
IR (KBr): 3363.2, 1454.1, 1101.2 cm^{-1}
NMR (CDCl_3 , δ): 0.87-2.08 (24H, m), 2.88-3.60 (4H, m)

Preparation 208

- 30 To a solution of 4'-propoxybicyclohexyl-4-ol (1 g) and triethylamine (0.81 ml) in dichloromethane (10 ml) was added dropwise methanesulfonyl chloride (0.39 ml) at 0-5°C, and stirred for 3 hours. The reaction mixture was washed with water and brine, and dried, and evaporated under reduced
35 pressure to give 4'-propoxy-4-methylsulfonyloxy-1,1'-

bicyclohexane (1.44 g).

IR (KBr): 1454.1, 1351.9, 1338.4, 1164.8, 1110.8 cm^{-1}

NMR (CDCl_3 , δ): 0.87-2.20 (23H, m), 2.89-3.44 (7H, m)

5 Preparation 209

A mixture of 4-piperazinybenzoic acid ethyl ester (1.03 g), 4'-propoxy-4-methylsulfonyloxy-1,1'-bicyclohexane (1.4 g), potassium carbonate (0.91 g) in N,N-dimethylformamide (10 ml) was stirred for 8 hours at 130°C. The reaction mixture was poured into water, and extracted with ethyl acetate. The organic layer was washed with brine and dried, and the solvent was evaporated under reduced pressure. The residue was chromatographed on a column of silica gel eluting with dichloromethane/methyl alcohol (200:1) to give 4-[4-(4'-propoxy-1,1'-bicyclohexan-4-yl)piperazin-1-yl]benzoic acid ethyl ester (0.26 g).

IR (KBr): 1706.7, 1286.3, 1108.9 cm^{-1}

NMR (CDCl_3 , δ): 0.88-2.20 (26H, m), 3.00-3.67 (11H, m), 4.33 (2H, q, $J=7.1\text{Hz}$), 6.85-6.89 (2H, m), 7.92-7.97 (2H, m)

MASS (m/z): 455

The following compound was obtained according to a similar manner to that of Preparation 171.

25

Preparation 210

4-[4-(4'-Propoxy-1,1'-bicyclohexan-4-yl)piperazin-1-yl]benzoic acid hydrochloride

IR (KBr): 1695.1, 1228.4, 1112.7 cm^{-1}

NMR (CDCl_3 , δ): 0.88-2.03 (23H, m), 3.10-3.66 (12H, m), 6.86-6.91 (2H, m), 7.98-8.02 (2H, m)

MASS (m/z): 455

The following compound was obtained according to a similar manner to that of Preparation 172.

35

Preparation 211

4-[4-(4'-Propoxy-1,1'-bicyclohexan-4-yl)piperazin-1-yl]benzoic acid benzotriazol-1-yl ester

- 5 IR (KBr): 1772.3, 1695.1, 1226.5, 1187.9, 1089.6 cm^{-1}
NMR (CDCl_3 , δ): 0.88-2.04 (23H, m), 3.10-3.69 (12H, m),
6.93-6.98 (2H, m), 7.39-8.17 (6H, m)

Preparation 212

- 10 Lithium aluminum hydride (7.94 g) was added slowly to stirred tetrahydrofuran (80 ml) at ambient temperature. To the mixture was added dropwise 3,3-tetramethyleneglutamide (7 g) in tetrahydrofuran (70 ml) at ambient temperature. After refluxed for 5 hours, to the reaction mixture was added
- 15 dropwise water, and the mixture was filtered. The filtrate was evaporated under reduced pressure to give an oil (4.7 g). To the residue was added tetrahydrofuran (47 ml) and triethylamine (6.12 ml). To the mixture was added dropwise benzyloxycarbonyl chloride (5.76 g) in tetrahydrofuran (6 ml)
- 20 at ambient temperature. After stirring for 1.5 hours, the reaction mixture was poured into water, and extracted with ethyl acetate. The organic layer was separated, washed with diluted hydrochloric acid, water, brine, and dried, and evaporated under reduced pressure to give an oil (8.52 g).
- 25 The oil was chromatographed on a silica gel eluting with a mixture of dichloromethane and methyl alcohol (100:1) to give an oil (5.51 g). A solution of this oil (5.51 g) in methyl alcohol (55 ml) was added 10% palladium on carbon (0.55 g), and hydrogen gas at atmospheric pressure for 6 hours. The
- 30 reaction mixture was filtered through celite and evaporated under reduced pressure to give 8-azaspiro[4.5]decane (2.49 g).

IR (KBr): 3249.5, 1531.2, 1467.6 cm^{-1}

NMR (CDCl_3 , δ): 1.40-1.64 (13H, m), 2.84 (4H, br s)

- 35 MASS (m/z): 140 ($M^+ + 1$)

The following compound was obtained according to a similar manner to that of Preparation 176.

5 Preparation 213

1-[4-[4-(8-Azaspiro[4.5]decan-8-yl)phenyl]piperazin-1-yl]ethanone

IR (KBr): 2937.1, 1648.8, 1515.8, 1238.1 cm^{-1}

10 NMR (CDCl_3 , δ): 1.42-1.67 (12H, m), 2.13 (3H, s), 3.03-3.08 (8H, m), 3.58-3.63 (2H, m), 3.73-3.79 (2H, m), 6.78-7.86 (4H, m)

MASS (m/z): 342 (M^+ +1)

15 The following compound was obtained according to a similar manner to that of Preparation 177.

Preparation 214

8-(Piperazinylphenyl)-8-azaspiro[4.5]decane

20 The following compound was obtained according to a similar manner to that of Preparation 170.

Preparation 215

25 4-[4-[4-(8-Azaspiro[4.5]decan-8-yl)phenyl]piperazin-1-yl]benzoic acid ethyl ester

IR (KBr): 1706.7, 1322.9, 1282.4, 1236.1, 1105.0 cm^{-1}

NMR (CDCl_3 , δ): 1.37 (3H, t, $J=7.1\text{Hz}$), 1.41-1.65 (12H, m), 3.03-3.09 (4H, m), 3.19-3.24 (4H, m), 3.45-3.50 (4H, m), 4.34 (2H, q, $J=7.1\text{Hz}$), 6.89-6.94 (6H, m), 7.93-7.97 (2H, m)

30 MASS (m/z): 448 (M^+ +1)

The following compound was obtained according to a similar manner to that of Preparation 171.

Preparation 216

4-[4-[4-(8-Azaspiro[4.5]decan-8-yl)phenyl]piperazin-1-yl]benzoic acid dihydrochloride

IR (KBr): 2946.7, 1689.3, 1388.5, 1226.5, 1184.1 cm^{-1}

5 NMR (DMSO- d_6 , δ): 1.40-2.40 (12H, m), 3.00-4.20 (12H, m), 7.01-7.15 (4H, m), 7.69-7.74 (2H, m), 7.78-7.83 (2H, m), 12.06 (1H, br s)

MASS (m/z): 420 (M^+ +1) (free)

10 The following compound was obtained according to a similar manner to that of Preparation 172.

Preparation 217

4-[4-[4-(8-Azaspiro[4.5]decan-8-yl)phenyl]piperazin-1-yl]benzoic acid benzotriazol-1-yl ester

15 IR (KBr): 1781.9, 1598.7, 1513.8, 1228.4 cm^{-1}

NMR (CDCl_3 , δ): 1.43-1.73 (2H, m), 3.05-3.10 (4H, m), 3.22-3.27 (4H, m), 3.59-3.64 (4H, m), 6.90-7.02 (6H, m), 7.39-7.58 (3H, m), 8.07-8.17 (3H, m)

20 MASS (m/z): 537 (M^+ +1)

Preparation 218

To a solution of 4-acetyl-1-(4-hydroxyphenyl)piperazine (20 g) and pyridine (11.02 ml) in dichloromethane (60 ml) was
25 added dropwise with stirring trifluoromethanesulfonic acid anhydride (20 ml) at 0°C. The mixture was then stirred for 1 hour at 0°C and 1 hour at room temperature. The reaction mixture was added to a mixture of 0.5 mol/l hydrochloric acid and dichloromethane. The organic layer was washed with
30 sodium hydrogen carbonate solution and sodium chloride solution. The organic layer was taken and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (30:1
35 dichloromethane-methanol elution). Diisopropyl ether was

added to the residue, and precipitates were filtered, washed with the same solvent, and dried to give trifluoromethanesulfonic acid 4-(4-acetylpiperazin-1-yl)phenyl ester (27.78 g).

- 5 NMR (CDCl₃, δ): 2.15 (3H, s), 3.20 (4H, m), 3.63 (2H, t, J=5.2Hz), 3.78 (2H, t, J=5.2Hz), 6.88-6.95 (2H, m), 7.15-7.20 (2H, m)
MASS (m/z): 353 (M⁺+1)

10 Preparation 219

To a mixture of cesium carbonate (25.32 g), palladium(II) acetate (0.624 g) and 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (2.59 g) in toluene (110 ml) was successively added cis-2,6-dimethylmorpholine (110 ml) and trifluoromethanesulfonic acid 4-(4-acetylpiperazin-1-yl)phenyl ester (20 g) in stream of nitrogen. The mixture was stirred at ambient temperature for 30 minutes and at 100°C for further 12 hours. After cooling to room temperature, water was added to the reaction mixture.

- 15 (8.21 ml) and trifluoromethanesulfonic acid 4-(4-acetylpiperazin-1-yl)phenyl ester (20 g) in stream of nitrogen. The mixture was stirred at ambient temperature for 30 minutes and at 100°C for further 12 hours. After cooling to room temperature, water was added to the reaction mixture.
20 The resulting precipitates were filtered, washed with water and dried. The residue was purified by silica gel chromatography (50:1 dichloromethane-methanol elution) to give 1-[4-[4-(cis-2,6-dimethylmorpholin-4-yl)phenyl]piperazin-1-yl]ethanone (7.78 g).

- 25 NMR (CDCl₃, δ): 1.15-1.30 (6H, m), 2.13 (3H, s), 2.36 (2H, t, J=11.1Hz), 3.00-3.90 (12H, m), 6.85-7.00 (4H, m)
MASS (m/z): 318 (M⁺+1)

30 Preparation 220

A mixture 1-[4-[4-(cis-2,6-dimethylmorpholin-4-yl)phenyl]piperazin-1-yl]ethanone (11.37 g) and 1.0 mol/l hydrochloric acid (225 ml) in ethanol (220 ml) was refluxed for 23 hours. The reaction mixture was added to a mixture of

- 35 1.0 mol/l sodium hydroxide solution and dichloromethane. The

organic layer was taken and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was concentrated under reduced pressure to give cis-2,6-dimethyl-4-(4-piperazinylphenyl)morpholine (3.64 g).

- 5 NMR (CDCl₃, δ): 1.24 (6H, d, J=6.3Hz), 2.35 (2H, t, J=11.1Hz), 2.95-3.40 (11H, m), 3.70-3.9 (2H, m), 6.8-6.95 (4H, m)
 MASS (m/z): 276 (M⁺+1)

10 Preparation 221

- A solution of cis-2,6-dimethyl-4-(4-piperazinylphenyl)morpholine (2.00 g), 4-fluorobenzoic acid ethyl ester (1.43 g) and potassium carbonate (1.01 g) in dimethylsulfoxide (40 ml) was stirred for 8 hours at 150°C, during which period additional 4-fluorobenzoic acid ethyl ester (1.35 g) and potassium carbonate (1.0 g) was added to the mixture. The reaction mixture was added to a mixture of water and dichloromethane. The organic layer was taken and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (25:1 dichloromethane-methanol elution) to give 4-[4-[4-(cis-2,6-dimethylmorpholin-4-yl)phenyl]piperazin-1-yl]benzoic acid ethyl ester (2.5 g).
- 15 IR (KBr): 1705, 1697 1605, 1513, 1282, 1234 cm⁻¹
 NMR (DMSO-d₆, δ): 1.25 (6H, d, J=6.3Hz), 1.36 (3H, t, J=7.1Hz), 2.37 (2H, t, J=11.1Hz), 3.15-3.55 (10H, m), 3.7-3.9 (2H, m), 4.34 (2H, q, J=7.1Hz), 6.85-7.00 (6H, m), 7.95 (2H, d, J=8.9Hz)
- 20 MASS (m/z): 424 (M⁺+1)
- 25 MASS (m/z): 424 (M⁺+1)

30 Preparation 222

- A mixture of 4-[4-[4-(cis-2,6-dimethylmorpholin-4-yl)phenyl]piperazin-1-yl]benzoic acid ethyl ester (2.46 g) and 1.0 mol/l sodium hydroxide solution (11.6 ml) in a mixed
- 35

solvent of ethanol (50 ml) and tetrahydrofuran (125 ml) was refluxed for 33 hours, during which period additional 1.0 mol/l sodium hydroxide solution (24 ml) was added to the mixture. After cooling to ambient temperature, the reaction mixture was poured into cold water, and the mixture was adjusted to pH 2 with 1.0 mol/l hydrochloric acid. The resulting precipitates were filtered, washed with water and dried to give 4-[4-[4-(cis-2,6-dimethylmorpholin-4-yl)phenyl]piperazin-1-yl]benzoic acid (1.05 g).

IR (KBr): 1664, 1603, 1514, 1234 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ): 1.14 (6H, d, $J=6.21\text{Hz}$), 2.16 (2H, t, $J=11.0\text{Hz}$), 3.05-3.80 (12H, m), 6.80-7.15 (6H, m), 7.79 (2H, d, $J=8.8\text{Hz}$)

MASS (m/z): 472 (M^++1)

Preparation 223

A mixture of 4-[4-[4-(cis-2,6-dimethylmorpholin-4-yl)phenyl]piperazin-1-yl]benzoic acid (1.01 g), 1-hydroxybenzotriazole (370 mg) and 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (986 mg) in methylene chloride (100 ml) was stirred for 4 hours at room temperature then evaporated under reduced pressure. Water was added to the residue and the resulting precipitate collected by filtration, washed with water, then dried under hi-vacuum to give 4-[4-[4-(cis-2,6-dimethylmorpholin-4-yl)phenyl]piperazin-1-yl]benzoic acid benzotriazol-1-yl ester (1.197 g).

IR (KBr): 1784, 1603, 1512, 1232 cm^{-1}

NMR (CDCl_3 , δ): 1.26 (6H, d, $J=6.3\text{Hz}$), 2.38 (2H, t, $J=11.0\text{Hz}$), 3.15-3.45 (6H, m), 3.62 (4H, t, $J=5.1\text{Hz}$), 3.7-3.95 (2H, m), 6.8-7.1 (6H, m), 7.3-7.6 (3H, m), 8.0-8.25 (3H, m)

MASS (m/z): 589 (M^++1)

Preparation 224

To a mixture of cesium carbonate (6.33 g), palladium(II) acetate (156 mg) and 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (648 mg) in dioxane (28 ml) was successively added
5 cis-2,6-dimethyl-4-(4-piperazinyphenyl)morpholine (4.59 g) and 4'-trifluoromethanesulfonyloxy-1,1'-biphenyl-4-carboxylic acid methyl ester (5 g) in a stream of nitrogen. The mixture was stirred at ambient temperature for 30 minutes and at 80°C for a further 28 hours. After cooling to room temperature,
10 water was added to the reaction mixture. The resulting precipitates were filtered, washed with water and dried to give 4'-[4-[4-(cis-2,6-dimethylmorpholin-4-yl)phenyl]-piperazin-1-yl]-1,1'-biphenyl-4-carboxylic acid methyl ester (3.72 g).

15 NMR (CDCl₃, δ): 1.26 (6H, d, J=6.3Hz), 2.37 (2H, t, J=11.0Hz), 3.2-3.5 (10H, m), 3.75-3.9 (2H, m), 3.93 (3H, s), 6.8-7.15 (6H, m), 7.5-7.7 (4H, m), 8.07 (2H, d, J=8.3Hz)

20 MASS (m/z): 486 (M⁺+1)

Preparation 225

A mixture of 4'-[4-[4-(cis-2,6-dimethylmorpholin-4-yl)phenyl]piperazin-1-yl]-1,1'-biphenyl-4-carboxylic acid methyl ester (3.70 g) and 1.0 mol/l sodium hydroxide solution
25 (30 ml) in a mixed solvent of methanol (75 ml) and tetrahydrofuran (185 ml) was refluxed for 15.5 hours. After cooling to ambient temperature, the reaction mixture was poured into cold water, and the mixture was adjusted to pH 2 with 1.0 mol/l hydrochloric acid. The resulting precipitates
30 were filtered, washed with water and diisopropyl ether and dried to give 4'-[4-[4-(cis-2,6-dimethylmorpholin-4-yl)phenyl]piperazin-1-yl]-1,1'-biphenyl-4-carboxylic acid (3.68 g).

35 MASS (m/z): 472 (M⁺+1)

The following compound was obtained according to a similar manner to that of Preparation 223.

Preparation 226

4'-[4-[4-(2,6-Dimethylmorpholin-4-yl)phenyl]piperazin-1-yl]-1,1'-biphenyl-4-carboxylic acid benzotriazol-1-yl ester

NMR (DMSO- d_6 , δ): 1.26 (6H, d, $J=6.3\text{Hz}$), 2.38 (2H, t, $J=11.0\text{Hz}$), 3.2-3.6 (10H, m), 3.7-3.95 (2H, m), 6.85-7.15 (6H, m), 7.4-7.9 (7H, m), 8.12 (2H, d, $J=8.1\text{Hz}$), 8.31 (2H, d, $J=8.5\text{Hz}$)

MASS (m/z): 589 ($M^+ + 1$)

Preparation 227

A solution of 4-fluorobenzoic acid ethyl ester (3 g), cis-2,6-dimethylmorpholine (2.26 g) and potassium carbonate (2.47 g) in dimethylsulfoxide (60 ml) was stirred for 18 hours at 80°C. The reaction mixture was added to a mixture of water and ethyl acetate. The organic layer was taken and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (5:1 hexane-ethyl acetate elution) to give 4-(cis-2,6-dimethylmorpholin-4-yl)benzoic acid ethyl ester (555 mg).

IR (KBr): 1695, 1605, 1518, 1244 cm^{-1}

NMR (CDCl_3 , δ): 1.27 (6H, d, $J=6.3\text{Hz}$), 1.37 (3H, t, $J=7.1\text{Hz}$), 2.51 (2H, t, $J=11.4\text{Hz}$), 3.5-3.9 (4H, m), 4.33 (2H, q, $J=7.1\text{Hz}$), 6.85 (2H, d, $J=9\text{Hz}$), 7.93 (2H, d, $J=8.9\text{Hz}$)

MASS (m/z): 250 ($M^+ + 1$)

Preparation 228

To a solution of 4-(cis-2,6-dimethylmorpholin-4-yl)benzoic acid ethyl ester (0.55 g) in a mixed solvent of methanol (3 ml) and tetrahydrofuran (6 ml) was added

hydrazine monohydrate (1.6 ml). The solution was refluxed for 20 hours, during which period additional hydrazine monohydrate (1.6 ml) was added to the mixture. After cooling to ambient temperature, the reaction mixture was added to a mixture of water and ethyl acetate. The organic layer was washed with sodium chloride solution. The organic layer was taken and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was concentrated under reduced pressure to give 4-(cis-2,6-dimethylmorpholin-4-yl)benzoic acid hydrazide (489.7 mg).

IR (KBr): 1632, 1606, 1506, 1331, 1246 cm^{-1}

NMR (DMSO- d_6 , δ): 1.15 (6H, d, $J=6.1\text{Hz}$), 2.3 (2H, t, $J=11.4\text{Hz}$), 3.55-3.8 (4H, m), 4.36 (2H, br s), 6.94 (2H, d, $J=8.9\text{Hz}$), 7.71 (2H, d, $J=8.8\text{Hz}$)

MASS (m/z): 250 ($M^+ + 1$)

Preparation 229

A mixture of 4-(cis-2,6-dimethylmorpholin-4-yl)benzoic acid hydrazide (458 mg), 4-methoxycarbonylbenzoyl chloride (622 mg) and pyridine (5 ml) in tetrahydrofuran (10 ml) was stirred for 6 hours at 0°C . The reaction mixture was added to water. The resulting precipitates were filtered, washed with water and dried to give 4-[N'-(4-(cis-2,6-dimethylmorpholin-4-yl)benzoyl)hydrazinocarbonyl]benzoic acid methyl ester (662.8 mg):

IR (KBr): 1724, 1606, 1279, 1242 cm^{-1}

NMR (DMSO- d_6 , δ): 1.17 (6H, d, $J=6.1\text{Hz}$), 2.35 (2H, t, $J=11.2\text{Hz}$), 3.6-3.85 (4H, m), 3.9 (3H, s), 7.02 (2H, d, $J=8.9\text{Hz}$), 7.83 (2H, d, $J=8.8\text{Hz}$), 8.0-8.2 (4H, m), 10.28 (1H, s), 10.58 (1H, s)

MASS (m/z): 412 ($M^+ + 1$)

Preparation 230

To a solution of 4-[N'-(4-(cis-2,6-dimethylmorpholin-4-yl)benzoyl)hydrazinocarbonyl]benzoic acid methyl ester (100

mg) in dimethoxyethane (3 ml) was added phosphorus pentasulfide (82 mg). The mixture was refluxed for 5 hours. After cooling to ambient temperature, the reaction mixture was poured into cold water and the mixture was adjusted to pH 11 with 1N-sodium hydroxide aqueous solution. The resulting precipitates were filtered, washed with water and dried to give 4-[5-[4-(cis-2,6-dimethylmorpholin-4-yl)phenyl][1,3,4]thiadiazol-2-yl]benzoic acid methyl ester (97.4 mg).

IR (KBr): 1716, 1605, 1437, 1412, 1277, 1238 cm^{-1}

NMR (CDCl_3 , δ): 1.29 (6H, d, $J=6.2\text{Hz}$), 2.54 (2H, t, $J=11.3\text{Hz}$), 3.61 (2H, d, $J=11.9\text{Hz}$), 3.7-3.9 (2H, m), 3.96 (3H, s), 6.96 (2H, d, $J=8.9\text{Hz}$), 7.91 (2H, d, $J=8.8\text{Hz}$), 8.0-8.25 (4H, m)

MASS (m/z): 410 ($M^+ + 1$)

Preparation 231

A mixture of 4-[5-[4-(cis-2,6-dimethylmorpholin-4-yl)phenyl][1,3,4]thiadiazol-2-yl]benzoic acid methyl ester (527 mg) and 1.0 mol/l sodium hydroxide solution (2.6 ml) in a mixed solvent of methanol (10 ml) and tetrahydrofuran (25 ml) was refluxed for 6 hours. After cooling to ambient temperature, the reaction mixture was poured into cold water and the mixture was adjusted with 1.0 mol/l hydrochloric acid. The resulting precipitates were filtered, washed with water and dried to give 4-[5-[4-(cis-2,6-dimethylmorpholin-4-yl)phenyl][1,3,4]thiadiazol-2-yl]benzoic acid (429.1 mg).

IR (KBr): 1686, 1605, 1412, 1236 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ): 1.18 (6H, d, $J=6.1\text{Hz}$), 2.39 (2H, t, $J=11.2\text{Hz}$), 3.6-3.9 (4H, m), 7.11 (2H, d, $J=9.1\text{Hz}$), 7.87 (2H, d, $J=8.8\text{Hz}$), 8.11 (4H, s), 13.3 (1H, br s)

MASS (m/z): 396 ($M^+ + 1$)

The following compound was obtained according to a

similar manner to that of Preparation 223.

Preparation 232

4-[5-[4-(cis-2,6-Dimethylmorpholin-4-yl)phenyl]-

[1,3,4]thiadiazol-2-yl]benzoic acid benzotriazol-1-yl ester

IR (KBr): 1780, 1603, 1441, 1414, 1230 cm^{-1}

NMR (CDCl_3 , δ): 1.3 (6H, d, $J=6.2\text{Hz}$), 2.45-2.65 (2H, m),

3.55-3.95 (4H, m), 6.97 (2H, d, $J=8.9\text{Hz}$), 7.4-7.7

(3H, m), 7.85-8.5 (7H, m)

MASS (m/z): 513 (M^++1)

Preparation 233

A mixture of cesium trichloride (5.0 g) in tetrahydrofuran (45 ml) was stirred at room temperature for 6 hours. 1,4-Dioxaspiro[4.5]decan-8-one (1.4 g) was added to the solution and stirred at room temperature for 1 hour. To the solution was added dropwise with stirring cyclohexylmagnesium chloride (2.0M solution in diethyl ether) (6.7 ml) at 0°C . The reaction mixture was quenched with 10% acetic acid aqueous solution. Diethyl ether was added to the solution. The organic layer was taken, washed with brine, sodium hydrogen carbonate solution, brine and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography to give 8-cyclohexyl-1,4-dioxaspiro[4.5]-decan-8-ol (1.266 g).

NMR (CDCl_3 , δ): 0.9-2.1 (19H, m), 3.85-4.05 (4H, m)

Preparation 234

To a solution of 8-cyclohexyl-1,4-dioxaspiro[4.5]decan-8-ol (1.143 g) and iodomethane (0.59 ml) in N,N-dimethylformamide (11 ml) was added sodium hydride (60% dispersion in mineral oil) (342 mg) at 0°C . The solution was stirred for 9 hours at 0°C , during which period additional iodomethane (0.59 ml) and sodium hydride (60% dispersion in

mineral oil) (344 mg) was added to the mixture. The reaction mixture was added to a mixture of water and dichloromethane.

The organic layer was washed with water. The organic layer was taken and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate elution) to give 8-cyclohexyl-8-methoxy-1,4-dioxaspiro[4.5]decane (1.201 g).

IR (NaCl): 1448, 1377, 1250 cm^{-1}

10 NMR (CDCl_3 , δ): 0.9-1.9 (19H, m), 3.11 (3H, s),
3.85-4.0 (4H, m)

MASS (m/z): 277 (M^+ +Na)

Preparation 235

15 A solution of 8-cyclohexyl-8-methoxy-1,4-dioxaspiro[4.5]decane (1.15g) and acetic acid (40 ml) in water was stirred at 100°C for 6 hours. After cooling to room temperature, the reaction mixture was added to a mixture of sodium hydrogen carbonate solution and diethyl ether. The organic layer was taken, washed with sodium hydrogen carbonate solution and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was concentrated under reduced pressure to give 1-methoxy-1,1'-bicyclohexane-4-one (1.018 g).

25 NMR (CDCl_3 , δ): 0.8-2.7 (19H, m), 3.22 (3H, s)

MASS (m/z): 233 (M^+ +Na)

Preparation 236

To an ice cooled solution of ethyl 4-(piperazin-1-yl)benzoate (1.23 g) and 1-methoxy-1,1'-bicyclohexane-4-one (916 mg) in a mixed solvent of methanol (20 ml), tetrahydrofuran (15 ml) and acetic acid (0.74 ml) was added sodium cyanoborohydride (301 mg) in a stream of nitrogen. The mixture was stirred at this temperature for 1.5 hours and at room temperature for 7.5 hours. The reaction mixture was

quenched with saturated aqueous sodium hydrogen carbonate solution. Dichloromethane was added to the solution. The organic layer was taken, washed with sodium hydrogen carbonate solution and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (3:1 hexane-methanol elution) to give 4-[4-(1-methoxy-1,1'-bicyclohexan-4-yl)piperazinyl]benzoic acid ethyl ester (801 mg).

IR (KBr): 1701, 1608, 1520 cm^{-1}

NMR (CDCl_3 , δ): 0.7-1.9 (22H, m), 2.1-2.4 (1H, m), 2.65-2.85 (4H, m), 3.10 (3H, s), 3.25-3.4 (4H, m), 4.32 (2H, q, $J=7.1\text{Hz}$), 6.86 (2H, d, $J=8.8\text{Hz}$), 7.92 (2H, d, $J=8.9\text{Hz}$)

MASS (m/z): 429 (M^++1)

The following compound was obtained according to a similar manner to that of Preparation 231.

Preparation 237

4-[4-(1-Methoxy-1,1'-bicyclohexyl-4-yl)piperazin-1-yl]benzoic acid

IR (KBr): 1689, 1610, 1232, 1186 cm^{-1}

MASS (m/z): 401 (M^++1)

The following compound was obtained according to a similar manner to that of Preparation 223.

Preparation 238

4-[4-(1-Methoxy-1,1'-bicyclohexyl-4-yl)piperazinyl]benzoic acid benzotriazol-1-yl ester

IR (KBr): 1782, 1603, 1522, 1232, 1186 cm^{-1}

NMR (CDCl_3 , δ): 0.7-2.1 (19H, m), 2.2-2.3 (1H, m), 2.7-2.9 (4H, m), 3.11 (3H, s), 3.4-3.55 (4H, m), 6.94 (2H, d, $J=9.1\text{Hz}$), 7.3-7.6 (3H, m), 8.0-8.2

(3H, m)

MASS (m/z): 518 ($M^+ + 1$)

The following compound was obtained according to a similar manner to that of Preparation 236.

Preparation 239

4-[4-(1-Methoxy-1,1'-bicyclohexyl-4-yl)piperazinyl]benzoic acid ethyl ester

IR (KBr): 1703, 1606, 1518, 1450, 1282, 1238 cm^{-1}
NMR (CDCl_3 , δ): 0.7-2.3 (23H, m), 2.55-2.7 (4H, m),
3.14 (3H, s), 3.25-3.45 (4H, m), 4.33 (2H, q,
 $J=7.1\text{Hz}$), 6.8-6.95 (2H, m), 7.85-8.05 (2H, m)
MASS (m/z): 429 ($M^+ + 1$)

The following compound was obtained according to a similar manner to that of Preparation 231.

Preparation 240

4-[4-(1-Methoxy-1,1'-bicyclohexyl-4-yl)piperazinyl]benzoic acid

IR (KBr): 1668, 1603, 1228, 1186 cm^{-1}
MASS (m/z): 401 ($M^+ + 1$)

The following compound was obtained according to a similar manner to that of Preparation 223.

Preparation 241

4-[4-(1-Methoxy-1,1'-bicyclohexyl-4-yl)piperazin-1-yl]benzoic acid benzotriazol-1-yl ester

IR (KBr): 1767, 1603, 1524, 1232, 1186 cm^{-1}
NMR (CDCl_3 , δ): 0.7-2.1 (19H, m), 2.15-2.3 (1H, m),
2.55-2.7 (4H, m), 3.15 (3H, s), 3.35-3.55 (4H, m),
6.95 (2H, d, $J=9.1\text{Hz}$), 7.35-7.6 (3H, m), 8.0-8.2 (3H, m)

MASS (m/z): 518 ($M^+ + 1$)

Preparation 242

A solution of piperazine (30.37 g), 4-fluorobenzoic acid
5 ethyl ester (20 g) and potassium carbonate (65.75 g) in
dimethylsulfoxide (100 ml) was stirred for 5.5 hours at
150°C. After cooling to the room temperature, water was
added to the solution. The resulting precipitate was
collected by filtration and dried to give ethyl 4-
10 piperazinylbenzoate (18.48 g).

NMR (CDCl₃, δ): 1.37 (3H, t, J=7.1Hz), 2.95-3.1 (4H, m),
3.2-3.4 (4H, m), 4.33 (2H, q, J=7.1Hz), 6.87 (2H,
d, J=9.0Hz), 7.85-8.0 (2H, m)

MASS (m/z): 235 ($M^+ + 1$)

The following compound was obtained according to a
similar manner to that of Preparation 236.

Preparation 243

20 4-[4-(4-tert-Butylcyclohexyl)piperazinyl]benzoic acid
ethyl ester

IR (KBr): 1699, 1606, 1282, 1234, 1190 cm⁻¹

NMR (CDCl₃, δ): 0.85 (9H, s), 0.9-1.45 (8H, m), 1.75-
2.05 (4H, m), 2.1-2.4 (1H, m), 2.71 (4H, t,
25 J=5.1Hz), 3.33 (4H, t, J=5.1Hz), 4.25-4.4 (2H, m),
6.86 (2H, d, J=9.0Hz), 7.85-8.0 (2H, m)

MASS (m/z): 373 ($M^+ + 1$)

The following compound was obtained according to a
30 similar manner to that of Preparation 231.

Preparation 244

4-[4-(4-tert-Butylcyclohexyl)piperazinyl]benzoic acid

IR (KBr): 1680, 1603 cm⁻¹

35 MASS (m/z): 345 ($M^+ + 1$)

The following compound was obtained according to a similar manner to that of Preparation 223.

5 Preparation 245

4-[4-(4-tert-Butylcyclohexyl)piperazinyl]benzoic acid
benzotriazol-1-yl ester

IR (KBr): 1788, 1593, 1232 cm^{-1}

10 NMR (CDCl_3 , δ): 0.86 (9H, s), 0.9-1.4 (5H, m), 1.7-2.4
(5H, m), 2.75 (4H, t, $J=5.0\text{Hz}$), 3.47 (4H, t,
 $J=5.1\text{Hz}$), 6.8-7.05 (2H, m), 7.35-7.6 (3H, m), 8.0-
8.25 (3H, m)

MASS (m/z): 462 (M^++1)

15 The following compound was obtained according to a similar manner to that of Preparation 236.

Preparation 246

20 4-[4-(4-tert-Butylcyclohexyl)piperazinyl]benzoic acid
ethyl ester

IR (KBr): 1701, 1606, 1282, 1248, 1192 cm^{-1}

25 NMR (CDCl_3 , δ): 0.84 (9H, s), 1.0-1.5 (10H, m), 1.9-2.25
(3H, m), 2.58 (4H, t, $J=5.1\text{Hz}$), 3.31 (4H, t,
 $J=5.1\text{Hz}$), 4.33 (2H, q, $J=7.1\text{Hz}$), 6.8-6.95 (2H, m),
7.85-8.0 (2H, m)

MASS (m/z): 373 (M^++1)

The following compound was obtained according to a similar manner to that of Preparation 231.

30

Preparation 247

4-[4-(4-tert-Butylcyclohexyl)piperazinyl]benzoic acid

IR (KBr): 1664, 1606, 1240 cm^{-1}

MASS (m/z): 345 (M^++1)

35

The following compound was obtained according to a similar manner to that of Preparation 223.

Preparation 248

- 5 4-[4-(4-tert-Butylcyclohexyl)piperazinyl]benzoic acid
benzotriazol-1-yl ester

IR (KBr): 1778, 1603, 1232 cm^{-1}

- NMR (DMSO- d_6 , δ): 0.86 (9H, s), 1.0-1.5 (7H, m),
1.95-2.3 (3H, m), 2.62 (4H, t, $J=5.1\text{Hz}$), 3.45 (4H,
10 t, $J=5.1\text{Hz}$), 6.95 (2H, d, $J=9.2\text{Hz}$), 7.35-7.6 (3H,
m), 8.05-8.2 (3H, m)

MASS (m/z): 462 ($M^+ + 1$)

Preparation 249

- 15 A mixture of 4-bromo-4'-hydroxy-1,1'-biphenyl (5 g),
cis-2,6-dimethylmorpholine, dichlorobis(tri-o-
tolylphosphine)-palladium(II) and lithium
bis(trimethylsilyl)amide (1.0 M solution in hexanes) (44 ml)
in toluene (25 ml) was stirred for 6 hours at 100°C. The
20 reaction mixture was added to a mixture of 1.0 mol/l
hydrochloric acid and dichloromethane. The organic layer was
washed with 1.0 mol/l hydrochloric acid, sodium hydrogen
carbonate solution and sodium chloride solution. The organic
layer was taken and dried over magnesium sulfate. The
25 magnesium sulfate was filtered off, and the filtrate was
concentrated under reduced pressure. The residue was
purified by silica gel chromatography (50:1 dichloromethane-
methanol elution) to give 4'-(cis-2,6-dimethylmorpholin-4-
yl)-1,1'-biphenyl-4-ol (1.49 g).
30 NMR (CDCl_3 , δ): 1.28 (6H, d, $J=6.3\text{Hz}$), 2.45 (2H, t,
 $J=11.2\text{Hz}$), 3.49 (2H, d, $J=10.6\text{Hz}$), 3.75-3.95 (2H,
m), 4.89 (1H, s), 6.8-7.0 (4H, m), 7.4-7.5 (4H, m)
MASS (m/z): 284 ($M^+ + 1$)

- 35 The following compound was obtained according to a

similar manner to that of Preparation 218.

Preparation 250

Trifluoromethanesulfonic acid 4'-(cis-2,6-
5 dimethylmorpholin-4-yl)-1,1'-biphenyl-4-yl ester
NMR (CDCl₃, δ): 1.28 (6H, d, J=6.3Hz), 2.47 (2H, t,
J=11.3Hz), 3.52 (2H, d, J=10.4Hz), 3.7-3.95 (2H,
m), 6.98 (2H, d, J=8.8Hz), 7.30 (2H, d, J=8.8Hz),
7.48 (2H, d, J=8.7Hz), 7.60 (2H, d, J=8.8Hz)
10 MASS (m/z): 416 (M⁺+1)

Preparation 251

To a mixture of cesium carbonate (1.43 g), palladium(II)
acetate (35 mg) and 2,2'-bis(diphenylphosphino)-1,1'-
15 binaphthyl (146 mg) in dioxane (6 ml) was successively added
trifluoromethanesulfonic acid 4'-(cis-2,6-dimethylmorpholin-
4-yl)-1,1'-biphenyl-4-yl ester (1.30 g) and ethyl 4-
piperazinylbenzoate (0.88 g) in a stream of nitrogen. The
mixture was stirred at ambient temperature for 30 minutes and
20 at 100°C for further 6.5 hours. After cooling to room
temperature, water was added to the reaction mixture. The
resulting precipitates were filtered, washed with water and
dried. The residue was pulverized with acetone and collected
by filtration to give 4-[4'-(cis-2,6-dimethylmorpholin-4-
25 yl)-1,1'-biphenyl-4-yl]piperazinyl]benzoic acid ethyl ester
(1.17 g).

IR (KBr): 1703, 1608, 1504, 1284, 1230 cm⁻¹
NMR (CDCl₃, δ): 1.28 (6H, d, J=6.3Hz), 1.38 (3H, t,
J=7.1Hz), 2.45 (2H, t, J=10.9Hz), 3.3-3.6 (10H, m),
30 3.7-3.95 (2H, m), 4.34 (2H, q, J=7.1Hz), 6.85-7.1
(6H, m), 7.45-7.6 (4H, m), 7.96 (2H, d, J=8.9Hz)
MASS (m/z): 500 (M⁺+1)

The following compound was obtained according to a
35 similar manner to that of Preparation 222.

Preparation 252

4-[4-[4'-(cis-2,6-Dimethylmorpholin-4-yl)-1,1'-biphenyl-4-yl]piperazinyl]benzoic acid

5 IR (KBr): 1668, 1603, 1504, 1230 cm^{-1}

MASS (m/z): 472 ($\text{M}^+ + 1$)

The following compound was obtained according to a similar manner to that of Preparation 223.

10

Preparation 253

4-[4-[4'-(cis-2,6-Dimethylmorpholin-4-yl)-1,1'-biphenyl-4-yl]piperazinyl]benzoic acid benzotriazol-1-yl ester

IR (KBr): 1765, 1601, 1502, 1230, 1184 cm^{-1}

15

NMR (CDCl_3 , δ): 1.28 (6H, d, $J=6.3\text{Hz}$), 2.45 (2H, t, $J=11.2\text{Hz}$), 3.35-3.95 (12H, m), 6.9-7.1 (6H, m), 7.4-7.6 (7H, m), 8.05-8.2 (3H, m)

MASS (m/z): 589 ($\text{M}^+ + 1$)

20

Preparation 254

A solution of 4-bromophenol (3 g) and 1,4-dibromobutane (6.2 ml) in N,N-dimethylformamide (30 ml) was treated with potassium carbonate (2.89 g) at room temperature for 27 hours. The mixture was diluted with ethyl acetate and washed with brine. The organic layer was dried over magnesium sulfate, filtered, and evaporated. The residue was purified by silica gel chromatography (25:1 hexane-ethyl acetate elution) to give 1-bromo-4-(4-bromobutoxy)benzene (3.09 g).

25

NMR (CDCl_3 , δ): 1.8-2.15 (4H, m), 3.48 (2H, t, $J=6.4\text{Hz}$), 3.96 (2H, t, $J=5.9\text{Hz}$), 6.7-6.85 (2H, m), 7.3-7.45 (2H, m)

30

Preparation 255

A solution of 1-bromo-4-(4-bromobutoxy)benzene (3.05 g) in methanol (30 ml) was treated with 28% sodium methoxide in

35

methanol (2.43 ml), and the solution was refluxed for 5 hours. After cooling, the reaction mixture was added to a mixture of water and ethyl acetate. The organic layer was washed with brine. The organic layer was taken and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (10:1 hexane-ethyl acetate elution) to give 1-bromo-4-(4-methoxybutoxy)benzene (1.95 g).

IR (NaCl): 1591, 1489, 1286, 1244 cm^{-1}

NMR (CDCl_3 , δ): 1.65-1.95 (4H, m), 3.35 (3H, s), 3.44 (2H, t, $J=6.1\text{Hz}$), 3.95 (2H, t, $J=6.1\text{Hz}$), 6.77 (2H, d, $J=8.9\text{Hz}$), 7.36 (2H, d, $J=8.9\text{Hz}$)

MASS (m/z): 282 ($\text{M}^+ + \text{Na}$)

Preparation 256

To the solution of 1-bromo-4-(4-methoxybutoxy)benzene (4.94 g) and magnesium (463 mg) in tetrahydrofuran (50 ml) was added iodine at room temperature. The solution was refluxed for 7.5 hours, during which period diiodoethane was added to the mixture. After cooling to 0°C , 4-[4-(4-oxopiperidin-1-yl)phenyl]piperazine-1-carboxylic acid benzyl ester (4.94 g) in tetrahydrofuran (20 ml) was added dropwise with stirring to the solution. The mixture was stirred at room temperature for 2 hours. The reaction mixture was added to a mixture of ammonium chloride solution and ethyl acetate.

The organic layer was taken, washed with brine, sodium hydrogen carbonate solution and brine and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (50:1 dichloromethane-methanol elution) to give 4-[4-[4-hydroxy-4-[4-(4-methoxybutoxy)phenyl]piperidin-1-yl]phenyl]piperazine-1-carboxylic acid benzyl ester (3.42 g).

NMR (CDCl_3 , δ): 1.65-2.0 (6H, m), 2.1-2.4 (2H, m),

2.95-3.3 (6H, m), 3.35 (3H, s), 3.35-3.75 (8H, m),
3.99 (2H, t, J=5.9Hz), 5.16 (2H, s), 6.8-7.05 (6H,
m), 7.3-7.5 (9H, m)

MASS (m/z): 574 ($M^+ + 1$)

5

Preparation 257

To a solution of 4-[4-[4-hydroxy-4-[4-(4-methoxybutoxy)phenyl]piperidin-1-yl]phenyl]piperazine-1-carboxylic acid benzyl ester (3.41 g) in dichloromethane (50 ml) was added trifluoroacetic acid (8.5 ml) at 0°C. The reaction mixture was stirred at 0°C for 1 hour and at room temperature for further 6 hours. To the reaction mixture was added 1 mol/ml sodium hydroxide solution (170 ml), dichloromethane (136 ml) and methanol (14 ml). The organic layer was washed with water and brine, dried over magnesium sulfate, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (50:1 dichloromethane-methanol elution) to give 4-[4-[4-[4-(4-methoxybutoxy)phenyl]-3,6-dihydro-2H-pyridin-1-yl]phenyl]piperazine-1-carboxylic acid benzyl ester (2.23 g).

IR (KBr): 1701, 1514, 1232 cm^{-1}

NMR (CDCl_3 , δ): 1.7-2.0 (4H, m), 2.65 (2H, br s), 2.95-3.15 (4H, m), 3.35 (3H, s), 3.35-3.9 (10H, m), 3.99 (2H, t, J=6.0Hz), 5.16 (2H, s), 6.18 (1H, m), 6.8-7.0 (6H, m), 7.3-7.45 (7H, m)

MASS (m/z): 556 ($M^+ + 1$)

Preparation 258

To a mixture of 4-[4-[4-[4-(4-methoxybutoxy)phenyl]-3,6-dihydro-2H-pyridin-1-yl]phenyl]piperazine-1-carboxylic acid benzyl ester (2.20 g) and ammonium formate (1.25 g) in 90% methanol (44 ml) and dioxane was added 10% palladium on carbon at room temperature. The reaction mixture was heated at 100°C for 2 hours. After cooling, the reaction mixture

was filtered and evaporated. Sodium hydrogen carbonate solution was added to the residue. And the resulting precipitate was collected by filtration, washed with water and dried under hi-vacuum to give 1-[4-[4-[4-(4-methoxybutoxy)phenyl]piperidin-1-yl]phenyl]piperazine (1.36 g).

IR (KBr): 1514, 1234 cm^{-1}

NMR (DMSO- d_6 , δ): 1.5-1.9 (8H, m), 2.5-3.0 (7H, m), 3.23 (3H, s), 3.1-4.1 (11H, m), 6.8-7.25 (8H, m)

MASS (m/z): 424 (M^+ +1)

The following compound was obtained according to a similar manner to that of Preparation 221.

Preparation 259

4-[4-[4-[4-(4-Methoxybutoxy)phenyl]piperidin-1-yl]phenyl]piperazin-1-yl]benzoic acid methyl ester

IR (KBr): 1711, 1606, 1514, 1282, 1227 cm^{-1}

NMR (CDCl_3 , δ): 1.38 (3H, t, $J=7.1\text{Hz}$), 1.65-2.0 (8H, m), 2.5-2.9 (3H, m), 3.5-3.8 (12H, m), 3.35 (3H, s), 3.97 (2H, t, $J=6.0\text{Hz}$), 4.34 (2H, q, $J=7.0\text{Hz}$), 6.8-7.2 (10H, m), 7.95 (2H, d, $J=8.8\text{Hz}$)

MASS (m/z): 572 (M^+ +1)

The following compound was obtained according to a similar manner to that of Preparation 222.

Preparation 260

4-[4-[4-[4-(4-Methoxybutoxy)phenyl]piperidin-1-yl]phenyl]piperazin-1-yl]benzoic acid

IR (KBr): 1514, 1228 cm^{-1}

MASS (m/z): 544 (M^+ +1)

The following compound was obtained according to a similar manner to that of Preparation 223.

Preparation 261

4-[4-[4-[4-(4-Methoxybutoxy)phenyl]piperidin-1-yl]phenyl]piperazin-1-yl]benzoic acid benzotriazol-1-yl ester

IR (KBr): 1514, 1230 cm^{-1}

- 5 NMR (CDCl_3 , δ): 1.6-2.0 (8H, m), 2.5-2.9 (3H, m),
3.2-3.8 (15H, m), 3.9-4.05 (2H, m), 6.8-7.3 (10H, m), 7.35-7.6 (3H, m), 8.05-8.25 (3H, m)
MASS (m/z): 661 ($\text{M}^+ + 1$)

- 10 The following compound was obtained according to a similar manner to that of Preparation 219.

Preparation 262

1-[4-[4-(6-Methoxyhexylthio)piperidin-1-yl]phenyl]piperazin-1-yl]ethanone

IR (KBr): 1622, 1516, 1448, 1242 cm^{-1}

- 15 NMR (CDCl_3 , δ): 1.3-1.9 (10H, m), 1.95-2.15 (5H, m), 2.57 (2H, t, $J=7.3\text{Hz}$), 2.6-2.85 (3H, m), 2.95-3.15 (4H, m), 3.25-3.85 (11H, m), 6.89 (4H, s)
20 MASS (m/z): 434 ($\text{M}^+ + 1$)

The following compound was obtained according to a similar manner to that of Preparation 220.

Preparation 263

1-[4-[4-(6-Methoxyhexylthio)piperidin-1-yl]phenyl]piperazine

IR (KBr): 1622, 1514, 1454, 1242, 1120 cm^{-1}

- 30 NMR (CDCl_3 , δ): 1.3-1.9 (10H, m), 1.95-2.15 (2H, m), 2.57 (2H, t, $J=7.3\text{Hz}$), 2.6-2.85 (3H, m), 3.04 (8H, s), 3.3-3.6 (7H, m), 6.89 (4H, s)
MASS (m/z): 392 ($\text{M}^+ + 1$)

- The following compound was obtained according to a similar manner to that of Preparation 221.
- 35

Preparation 264

4-[4-[4-(6-Methoxyhexylthio)piperidin-1-yl]phenyl]piperazin-1-yl]benzoic acid ethyl ester

- 5 NMR (CDCl₃, δ): 1.3-1.9 (13H, m), 1.95-2.15 (2H, m),
2.57 (2H, t, J=7.3Hz), 2.6-2.85 (3H, m), 3.15-3.6
(15H, m), 4.34 (2H, q, J=7.0Hz), 6.85-7.0 (6H, m),
7.95 (2H, d, J=8.8Hz)
MASS (m/z): 540 (M⁺+1)

10

The following compound was obtained according to a similar manner to that of Preparation 222.

Preparation 265

15 4-[4-[4-(6-Methoxyhexylthio)piperidin-1-yl]phenyl]piperazin-1-yl]benzoic acid

IR (KBr): 1605, 1587, 1546, 1514, 1408, 1225 cm⁻¹
MASS (m/z): 512 (M⁺+1)

20

The following compound was obtained according to a similar manner to that of Preparation 223.

Preparation 266

25 4-[4-[4-(6-Methoxyhexylthio)piperidin-1-yl]phenyl]-piperazin-1-yl]benzoic acid benzotriazol-1-yl ester

IR (KBr): 1782, 1601, 1514, 1446, 1230, 1184 cm⁻¹
NMR (CDCl₃, δ): 1.3-1.9 (10H, m), 1.95-2.15 (2H, m),
2.58 (2H, t, J=7.3Hz), 2.65-2.85 (3H, m), 3.15-3.7
(15H, m), 6.85-7.1 (6H, m), 7.35-7.6 (3H, m), 8.05-
8.2 (3H, m)
MASS (m/z): 629 (M⁺+1)

30

The following compound was obtained according to a similar manner to that of Preparation 254.

35

Preparation 267

4-(4-Bromobutoxy)benzonitrile

IR (KBr): 2222, 1605, 1506, 1302, 1252 cm^{-1} NMR (CDCl_3 , δ): 1.9-2.2 (4H, m), 3.49 (2H, t, $J=6.2\text{Hz}$),
4.05 (2H, t, $J=5.7\text{Hz}$), 6.85-7.0 (2H, m), 7.5-7.65
(2H, m)MASS (m/z): 254 (M^+)

The following compound was obtained according to a
similar manner to that of Preparation 256.

Preparation 268

4-(4-Methoxybutoxy)benzonitrile

IR (KBr): 2216, 1605, 1570, 1510, 1468, 1308, 1261 cm^{-1} NMR (CDCl_3 , δ): 1.65-2.0 (4H, m), 3.35 (3H, s), 3.44
(2H, t, $J=6.1\text{Hz}$), 4.00 (2H, t, $J=6.2\text{Hz}$), 6.85-7.0
(2H, m), 7.5-7.65 (2H, m)MASS (m/z): 206 ($M^+ + 1$)Preparation 269

To a solution of 4-(4-methoxybutoxy)benzonitrile (21.8 g) and trifluoroacetic acid (109 ml) in toluene (218 ml) was added thiosemicarbazide (11.62 g). The solution was stirred for 31 hours at 60°C, during which period additional thiosemicarbazide (2.90 g) and trifluoroacetic acid was added to the mixture. The reaction mixture was pulverized with ethyl acetate. The precipitate was collected by filtration and dried to give 5-[4-(4-methoxybutoxy)phenyl]-[1,3,4]thiadiazol-2-ylamine trifluoroacetic acid salt (15.10 g).

IR (KBr): 1674, 1606, 1400 cm^{-1} NMR (CDCl_3 , δ): 1.55-2.0 (4H, m), 3.36 (3H, s), 3.45
(2H, t, $J=6.0\text{Hz}$), 4.04 (2H, t, $J=6.1\text{Hz}$), 4.41 (4H, br s), 6.95 (2H, d, $J=8.7\text{Hz}$), 7.63 (2H, d, $J=8.7\text{Hz}$)MASS (m/z): 280

Preparation 270

To a suspension of 5-[4-(4-methoxybutoxy)phenyl]-[1,3,4]thiadiazol-2-ylamine trifluoroacetic acid salt (45.00 g) in ethanol (450 ml) was added ethyl 4-bromoacetylbenzoate (28.85g), and the mixture was stirred under reflux for 4 hours. The reaction mixture was pulverized with ethyl acetate. The precipitate was collected by filtration and dried. To a suspension of the powder in xylene (450 ml) was added trifluoroacetic acid (67.5 ml), and the mixture was stirred at 130°C for 4 hours. The reaction mixture was pulverized with diisopropyl ether. The precipitate was collected by filtration and dried. The residue was pulverized with ethyl acetate, and the precipitate was collected by filtration and dried to give 4-[2-[4-(4-methoxybutoxy)phenyl]imidazo[2,1-b][1,3,4]thiadiazol-6-yl]benzoic acid ethyl ester (29.85 g).

NMR (CDCl₃, δ): 1.41 (3H, t, J=7.1Hz), 1.65-2.0 (4H, m), 3.36 (3H, s), 3.4-3.55 (2H, m), 4.0-4.15 (2H, m), 4.39 (2H, q, J=7.1Hz), 6.99 (2H, d, J=8.8Hz), 7.55-8.15 (7H, m)

MASS (m/z): 452 (M⁺+1)

The following compound was obtained according to a similar manner to that of Preparation 231.

Preparation 271

4-[2-[4-(4-Methoxybutoxy)phenyl]imidazo[2,1-b][1,3,4]-thiadiazol-6-yl]benzoic acid

IR (KBr): 1680, 1608, 1591, 1549, 1468, 1404, 1257 cm⁻¹

NMR (DMSO-d₆, δ): 1.55-1.9 (4H, m), 3.24 (3H, s), 3.3-3.5 (2H, m), 4.10 (2H, t, J=5.9Hz), 7.14 (2H, d, J=8.7Hz), 7.8-8.05 (6H, m), 8.84 (1H, s)

MASS (m/z): 424 (M⁺+1)

The following compound was obtained according to a similar manner to that of Preparation 223.

Preparation 272

- 5 4-[2-[4-[4-Methoxybutoxy)phenyl]imidazo[2,1-b][1,3,4]-
thiadiazol-6-yl]benzoic acid benzotriazol-1-yl ester
IR (KBr): 1768, 1606, 1547, 1470, 1404, 1255, 1176 cm^{-1}
NMR (CDCl_3 , δ): 1.6-2.0 (4H, m), 3.37 (3H, s), 3.47 (3H, t, $J=6.0\text{Hz}$), 4.08 (3H, t, $J=6.1\text{Hz}$), 7.02 (2H, d, $J=8.7\text{Hz}$), 7.4-7.65 (3H, m), 7.7-8.4 (8H, m)
10 MASS (m/z): 541 (M^++1)

Preparation 273

- A solution of oxalyl dichloride (597 μl) in dry
15 dichloromethane (7 ml) was cooled to -70°C in nitrogen
atmosphere, and a solution of dimethylsulfoxide (1.15 ml) in
dry dichloromethane (1.5 ml) was added slowly and stirred for
30 minutes at -70°C . To the reaction mixture was added a
solution of (3-hydroxypropyl)carbamic acid tert-butyl ester
20 (1.0 g) in dry dichloromethane (7 ml) slowly to maintain the
reaction temperature at -60°C and stirred for 30 minutes at
 -70°C . To the reaction mixture was added triethylamine (3.98
ml) slowly to maintain the reaction temperature at -60°C .
Then the reaction mixture was allowed to warm to room
25 temperature. To the reaction mixture was added water (10 ml)
and stirred for 10 minutes, then the organic layer was
separated. The aqueous layer was extracted with
dichloromethane (50 ml x 2). The organic layer was combined
and washed with brine, dried over magnesium sulfate.
30 Magnesium sulfate was filtered off, and the filtrate was
evaporated under reduced pressure to give 3-tert-
butoxycarbonylaminopropionaldehyde (1.28 g), that was used
crude in the next reaction.

- 35 The following compound was obtained according to a

similar manner to that of Preparation 273.

Preparation 274

5 5-tert-Butoxycarbonylaminovaleraldehyde, that was used
crude in the next reaction.

The following compound was obtained according to a
similar manner to that of Preparation 273.

10 Preparation 275

6-tert-Butoxycarbonylaminovaleraldehyde, that was used
crude in the next reaction.

The following compound was obtained according to a
15 similar manner to that of Preparation 273.

Preparation 276

4-tert-Butoxycarbonylaminovaleraldehyde, that was used
crude in the next reaction.

20

Preparation 277

To an ice-cooled solution of 5-aminopentan-1-ol (5.0 g)
in water (40 ml) and acetone (40 ml) was added triethylamine
(8.78 g) and di-tert-butyl dicarbonate (13.75 g), then the
25 solution was stirred at 30°C for 3 hours. The solvent was
evaporated under reduced pressure and extracted with ethyl
acetate. The organic layer was washed with water and brine,
then dried over magnesium sulfate. Magnesium sulfate was
filtered off, and the filtrate was evaporated under reduced
30 pressure to give a crude yellow oil (12.7 g). The crude oil
was purified by silica gel chromatography (50:1 - 4:1
dichloromethane-methanol) to give 5-hydroxypentylcarbamic
acid tert-butyl ester (8.68 g), as a pale yellow oil.

IR (KBr): 3344.0, 2975.6, 2935.1, 2865.7, 1706.7,
35 1695.1, 1529.3, 1280.5, 1249.6, 1178.3,

1168.7 cm^{-1}

NMR (DMSO-d_6 , δ): 1.1-1.6 (15H, m), 2.88 (2H, dd, $J=6.5$
and 12.6Hz), 3.2-3.5 (2H, m), 4.33 (1H, t,
 $J=5.1\text{Hz}$), 6.75 (1H, m)

5

The following compound was obtained according to a
similar manner to that of Preparation 277.

Preparation 278

10

6-Hydroxyhexylcarbamic acid tert-butyl ester

IR (KBr): 3351.7, 2977.6, 2937.1, 2859.9, 1714.4,
1679.7, 1533.1, 1276.6, 1249.6, 1180.2,
1164.8 cm^{-1}

15

NMR (DMSO-d_6 , δ): 1.0-1.6 (17H, m), 4.83 (2H, dd, $J=6.5$
and 12.8Hz), 3.2-3.59 (2H, m), 4.32 (1H, t,
 $J=5.2\text{Hz}$), 6.75 (1H, m)

The following compound was obtained according to a
similar manner to that of Preparation 277.

20

Preparation 279

(S)-(-)-4-tert-Butoxycarbonylamino-2-hydroxybutyric acid

NMR (DMSO-d_6 , δ): 1.37 (9H, s), 1.4-1.9 (2H, m), 3.00
(2H, dd, $J=7.0$ and 13.3Hz), 3.92 (1H, dd, $J=4.0$ and
8.4Hz), 6.78 (1H, m)

25

Preparation 280

To a solution of pyridinium chlorochromate (2.0 g) in
dichloromethane (15 ml) was added a solution of 6-
30 hydroxyhexanoic acid ethyl ester (1.0 g) in dichloromethane
(1.5 ml) in one portion and stirred for 1.5 hours at ambient
temperature. Ether (15 ml) was added to the reaction
mixture, and the insoluble material removed by filtration and
discarded. The filtrate was purified by silica gel
35 chromatography (diethyl ether) to give 6-oxohexanoic acid

ethyl ester (884.6 mg), as a pale green oil.

IR (KBr): 2981.4, 2940.9, 2871.5, 2827.1, 2723.0,
1731.8, 1184.1 cm^{-1}

NMR (CDCl_3 , δ): 1.26 (3H, t, $J=7.1\text{Hz}$), 1.5-1.8 (4H, m),
2.2-2.6 (4H, m), 4.13 (2H, q, $J=7.1\text{Hz}$), 9.77 (1H,
t, $J=1.6\text{Hz}$)

The following compound was obtained according to a
similar manner to that of Preparation 280.

Preparation 281

9-Oxo-nonanic acid methyl ester

IR (KBr): 2933.2, 2858.0, 2721.1, 1743.3, 1724.0,
1538.6, 1245.8, 1199.5, 1172.5 cm^{-1}

NMR (CDCl_3 , δ): 1.24 (6H, s), 1.3-1.7 (4H, m), 2.18 (2H,
t, $J=7.3\text{Hz}$), 2.29 (2H, t, $J=7.3\text{Hz}$), 3.58 (3H, s),
11.97 (1H, s)

Preparation 282

A solution of N-t-butoxycarbonyl-L-glutamic acid α -t-butyl ester (600 mg) and 4-piperidone hydrochloride monohydrate (455.6 mg) in dichloromethane (6 ml) - DMF (6 ml), was treated with 1-hydroxybenzotriazole (294 mg) and 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide (460.5 mg) and stirred 15 hours at room temperature. The reaction was diluted with ethyl acetate and washed with water, dried over magnesium sulfate, evaporated, and the residue was purified by silica gel column chromatography (EtOAc elution) to give 4-(4-piperidon-1-yl)carbonyl-2-tert-butoxycarbonylamino-butanoic acid tert-butyl ester (450 mg) as a white solid.

IR (KBr): 3381, 2931, 2883, 1707, 1631.5, 1510, 1448,
1367, 1321 cm^{-1}

NMR (CDCl_3 , δ): 1.43 (9H, s), 1.48 (9H, s), 1.85-2.10
(1H, m), 2.15-2.4 (1H, m), 2.4-2.6 (6H, m), 3.6-4.1
(4H, m), 4.1-4.3 (1H, m), 5.19 (1H, br d, $J=8.4\text{Hz}$)

The following compound was obtained according to a similar manner to that of Preparation 282.

5 Preparation 283

1-(1-tert-Butoxycarbonylazetidino-3-yl)carbonyl-4-piperidone

IR (KBr): 2979.5, 2891, 1712.5, 1691.3, 1649 cm^{-1}

10 NMR (CDCl_3 , δ): 1.44 (9H, s), 2.44-2.53 (4H, m),
3.54-3.61 (3H, m), 3.89-3.95 (2H, m), 4.06-4.22 (4H, m)

MASS (m/z): 305.2 ($\text{M}^+ + \text{Na}$)

Elemental Analysis Calcd. for $\text{C}_{14}\text{H}_{22}\text{N}_2\text{O}_4 \cdot 0.6\text{H}_2\text{O}$:

C 57.36, H 7.98, N 9.56

15 Found: C 57.29, H 7.65, N 9.58

Preparation 284

To a solution of 1,3-dioxo-5-hydroxymethyl-4-methyl-2-oxo-4-cyclopentene (2 g) and N,N'-disuccinimidyl carbonate (4.33 g) in dimethylformamide (10 ml) was added pyridine (1.37 ml) and stirred at ambient temperature. The reaction mixture was added to a mixture of water and ethyl acetate. The organic layer was taken and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was
25 evaporated under reduced pressure to give (1,3-dioxo-2-oxo-4-cyclopenten-5-yl)methoxycarbonyloxysuccinimido (2.477 g).

IR (KBr): 1808.8, 1785.8, 1741.4, 1733.7, 1259.3,
1228.4, 1209.1 cm^{-1}

30 NMR (CDCl_3 , δ): 2.20 (3H, s), 2.86 (4H, s), 5.06 (2H, s)
ESI-MASS (m/z): 294.1 ($\text{M}^+ + \text{Na} + 1$)

Preparation 285

To a solution of 1-methyl-4-piperidone (1.0 g) in N,N-dimethylformamide (10 ml) was added 2-iodoethanol (0.70
35 ml - 1.5 g) and stirred overnight at ambient temperature.

The reaction mixture was evaporated under reduced pressure and washed by ethyl acetate to afford 1-(2-hydroxyethyl)-1-methyl-4-oxopiperidinium iodide (0.94 g).

MASS (m/z): 158 ($M^+ - I^-$)

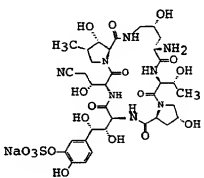
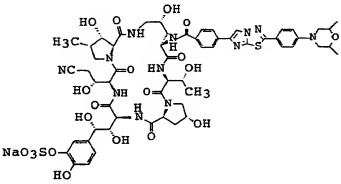
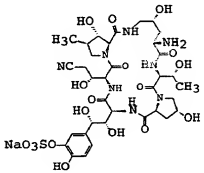
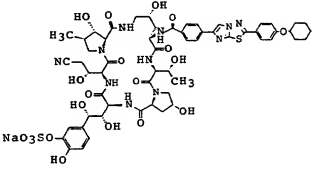
Preparation 286

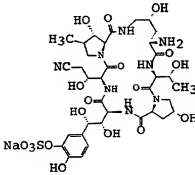
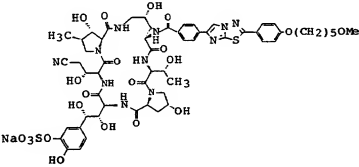
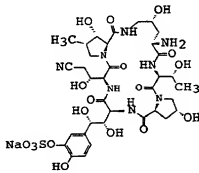
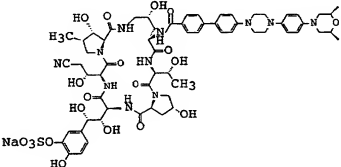
To a solution of 1-methyl-4-piperidone (1.0 g) in dichloromethane (5 ml) was slowly added iodomethane (1 ml) at 0°C and stirred for 30 minutes at ambient temperature. To the reaction mixture was added isopropyl ether (10 ml), and the resulting precipitate was collected by filtration to give 1,1-dimethyl-4-oxopiperidinium iodide (1.416 g).

NMR (DMSO- d_6 , δ): 1.87 (2H, t, $J=5.4$ Hz), 2.71 (2H, t, $J=6.4$ Hz), 3.09 (3H, s), 3.27 (3H, s), 3.30-3.40 (2H, m), 3.75 (2H, t, $J=6.6$ Hz)

The Starting Compounds (287) to (290) used and the Object Compounds (287) to (290) obtained in the following Preparations 287 to 290 are given in the table as below, in which the formulas of the starting compounds are in the upper column and the formulas of the object compounds are in the lower column, respectively.

to be continued on the next page

Preparation No.	Formula
287	
	
288	
	

Preparation No.	Formula
289	
	
290	
	

The following compounds [Preparations 287 to 290] were obtained according to a similar manner to that of Preparation 10.

5

Preparation 287MASS (m/z): 1317.3 (M^+ -Na)Preparation 288

10

MASS (m/z): 1302.3 (M^+ -Na)Preparation 289MASS (m/z): 1320.3 (M^+ -Na)

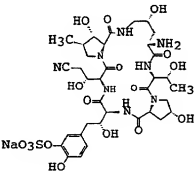
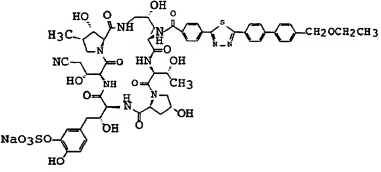
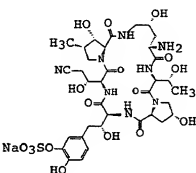
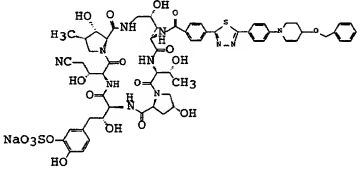
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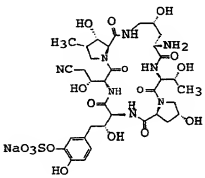
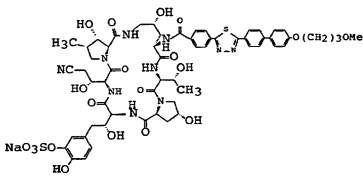
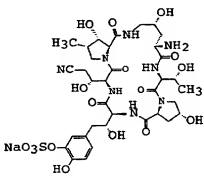
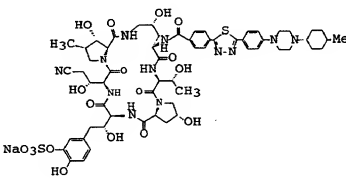
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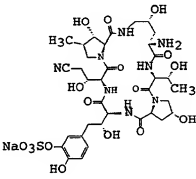
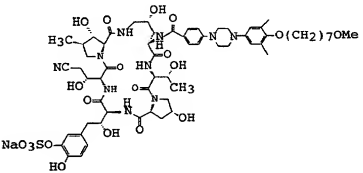
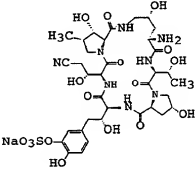
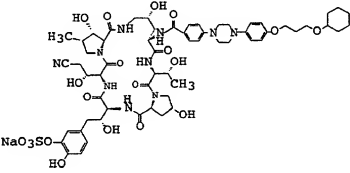
The object compound was used directly in the next reaction without purification.

20

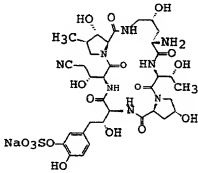
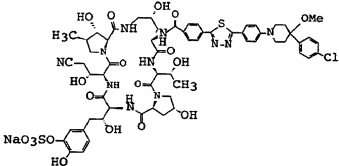
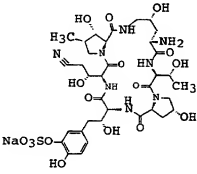
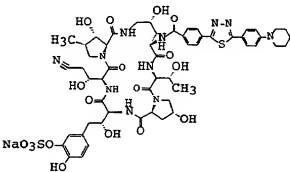
The Starting Compounds (291) to (338) used and the Object Compounds (291) to (338) obtained in the following Preparation 291 to 338 are given in the table as below, in which the formulas of the starting compounds are in the upper column and the formulas of the object compounds are in the lower column, respectively.

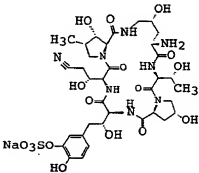
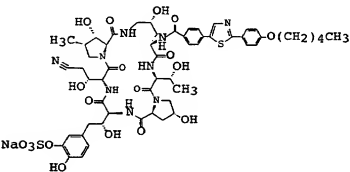
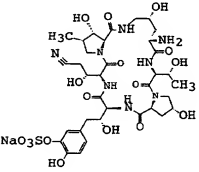
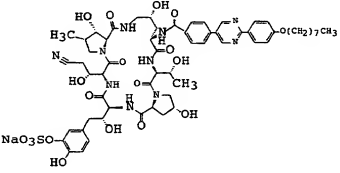
Preparation No.	Formula
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292	
	

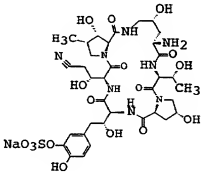
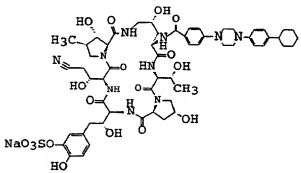
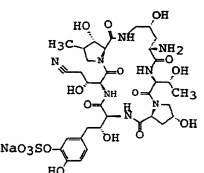
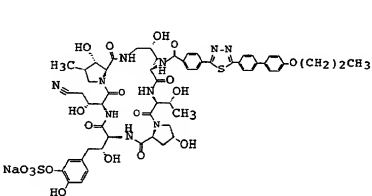
Preparation No.	Formula
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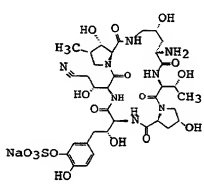
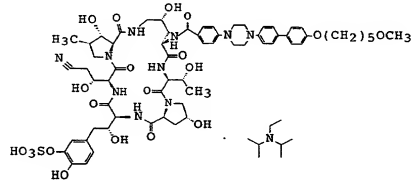
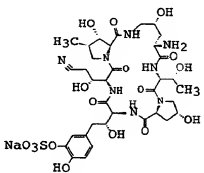
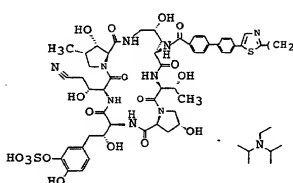
Preparation No.	Formula
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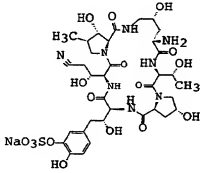
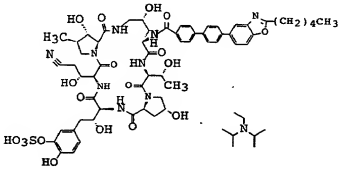
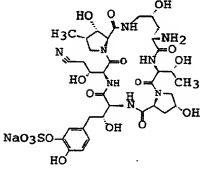
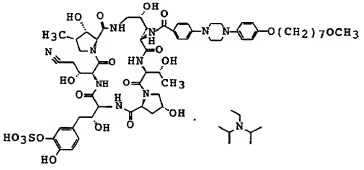
Preparation No.	Formula
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298	

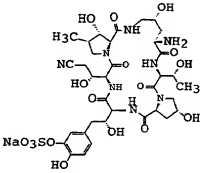
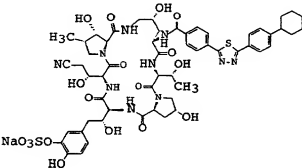
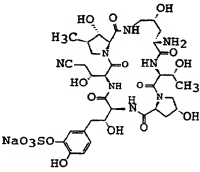
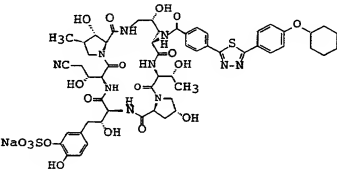
Preparation No.	Formula
299	 <p>Chemical structure of compound 299: A complex molecule featuring a central core with multiple hydroxyl groups, a methyl group, and a sodium sulfonate group (NaO₃SO₃) attached to a phenyl ring. The structure includes several amide and ester linkages, and a terminal amino group (NH₂).</p>
	 <p>Chemical structure of compound 299: A complex molecule featuring a central core with multiple hydroxyl groups, a methyl group, and a sodium sulfonate group (NaO₃SO₃) attached to a phenyl ring. The structure includes several amide and ester linkages, and a terminal amino group (NH₂). It also features a thioether linkage to a phenyl ring with a methoxy group (OMe) and a chlorine atom (Cl).</p>
300	 <p>Chemical structure of compound 300: A complex molecule featuring a central core with multiple hydroxyl groups, a methyl group, and a sodium sulfonate group (NaO₃SO₃) attached to a phenyl ring. The structure includes several amide and ester linkages, and a terminal amino group (NH₂).</p>
	 <p>Chemical structure of compound 300: A complex molecule featuring a central core with multiple hydroxyl groups, a methyl group, and a sodium sulfonate group (NaO₃SO₃) attached to a phenyl ring. The structure includes several amide and ester linkages, and a terminal amino group (NH₂). It also features a thioether linkage to a phenyl ring with a methoxy group (OMe) and a chlorine atom (Cl).</p>

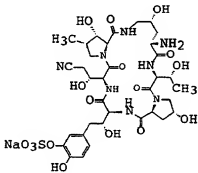
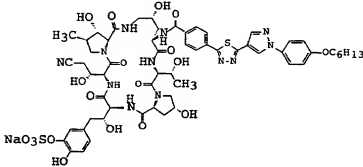
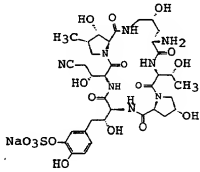
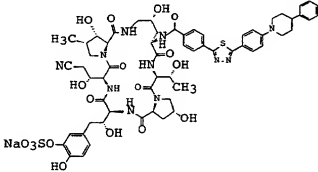
Preparation No.	Formula
301	 <p>Chemical structure of compound 301: A complex molecule featuring a central core with multiple hydroxyl groups, a nitrile group, and a sodium sulfonate group (NaO₃SO₃-) attached to a phenyl ring. The structure includes several amide and ester linkages, and a terminal hydroxyl group.</p>
	 <p>Chemical structure of compound 301: A complex molecule featuring a central core with multiple hydroxyl groups, a nitrile group, and a sodium sulfonate group (NaO₃SO₃-) attached to a phenyl ring. The structure includes several amide and ester linkages, and a terminal hydroxyl group.</p>
302	 <p>Chemical structure of compound 302: A complex molecule featuring a central core with multiple hydroxyl groups, a nitrile group, and a sodium sulfonate group (NaO₃SO₃-) attached to a phenyl ring. The structure includes several amide and ester linkages, and a terminal hydroxyl group.</p>
	 <p>Chemical structure of compound 302: A complex molecule featuring a central core with multiple hydroxyl groups, a nitrile group, and a sodium sulfonate group (NaO₃SO₃-) attached to a phenyl ring. The structure includes several amide and ester linkages, and a terminal hydroxyl group.</p>

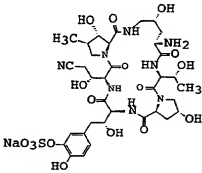
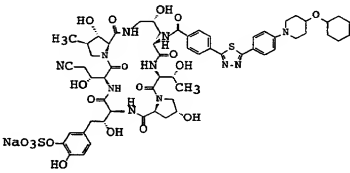
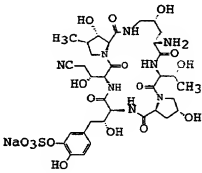
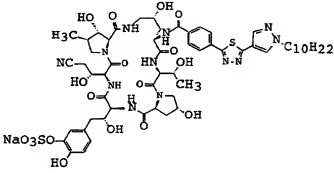
Preparation No.	Formula
303	
	
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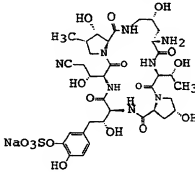
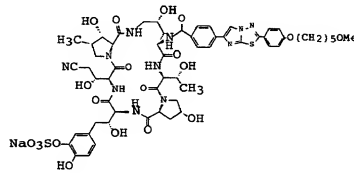
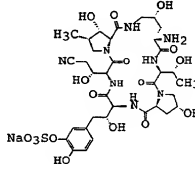
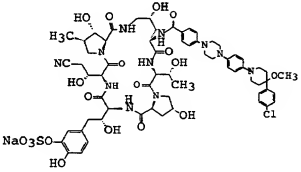
Preparation No.	Formula
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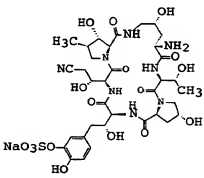
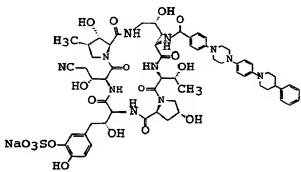
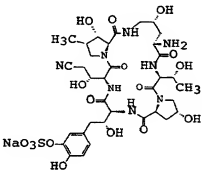
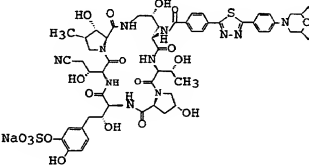
Preparation No.	Formula
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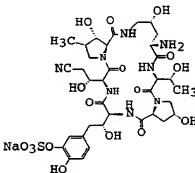
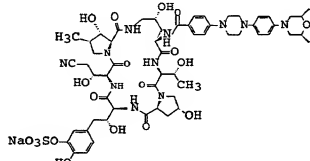
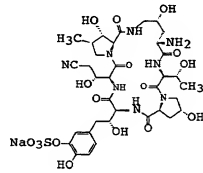
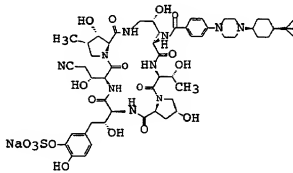
Preparation No.	Formula
309	 <p>Chemical structure of Preparation 309, Formula 1. It is a complex molecule featuring a central core with multiple hydroxyl groups, a methyl group, a nitrile group, and a sodium sulfonate group. The structure includes a benzene ring with a hydroxyl group and a sodium sulfonate group, connected to a complex polycyclic system.</p>
	 <p>Chemical structure of Preparation 309, Formula 2. It is a complex molecule featuring a central core with multiple hydroxyl groups, a methyl group, a nitrile group, and a sodium sulfonate group. The structure includes a benzene ring with a hydroxyl group and a sodium sulfonate group, connected to a complex polycyclic system, and a cyclohexyl group.</p>
310	 <p>Chemical structure of Preparation 310, Formula 1. It is a complex molecule featuring a central core with multiple hydroxyl groups, a methyl group, a nitrile group, and a sodium sulfonate group. The structure includes a benzene ring with a hydroxyl group and a sodium sulfonate group, connected to a complex polycyclic system.</p>
	 <p>Chemical structure of Preparation 310, Formula 2. It is a complex molecule featuring a central core with multiple hydroxyl groups, a methyl group, a nitrile group, and a sodium sulfonate group. The structure includes a benzene ring with a hydroxyl group and a sodium sulfonate group, connected to a complex polycyclic system, and a cyclohexyl group.</p>

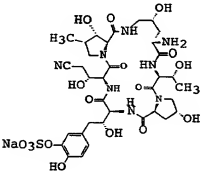
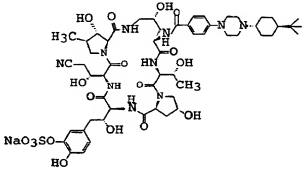
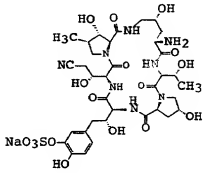
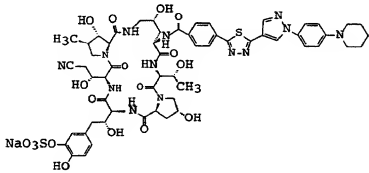
Preparation No.	Formula
311	 <p>Chemical structure of compound 311: A complex molecule featuring a central core with multiple hydroxyl groups, a methyl group, a nitrile group, and a sodium sulfonate group (NaO₃SO) attached to a phenyl ring. The structure includes several amide and ester linkages.</p>
	 <p>Chemical structure of compound 311 (continued): This structure shows a more complex derivative of the core molecule, featuring a central core with multiple hydroxyl groups, a methyl group, a nitrile group, and a sodium sulfonate group (NaO₃SO) attached to a phenyl ring. It also includes a thioether linkage and a long aliphatic chain (OC₆H₁₃).</p>
312	 <p>Chemical structure of compound 312: A complex molecule featuring a central core with multiple hydroxyl groups, a methyl group, a nitrile group, and a sodium sulfonate group (NaO₃SO) attached to a phenyl ring. The structure includes several amide and ester linkages.</p>
	 <p>Chemical structure of compound 312 (continued): This structure shows a more complex derivative of the core molecule, featuring a central core with multiple hydroxyl groups, a methyl group, a nitrile group, and a sodium sulfonate group (NaO₃SO) attached to a phenyl ring. It also includes a thioether linkage and a long aliphatic chain (OC₆H₁₃).</p>

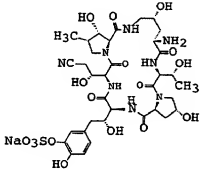
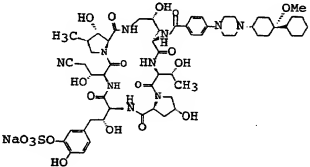
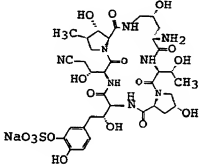
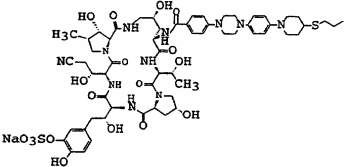
Preparation No.	Formula
313	 <p>Chemical structure of compound 313: A complex molecule featuring a central core with multiple hydroxyl groups, a sodium sulfonate group (NaO₃SO), and a hydroxyl group. The structure includes a pyrazole ring system and a sulfonate group.</p>
	 <p>Chemical structure of compound 313: A complex molecule featuring a central core with multiple hydroxyl groups, a sodium sulfonate group (NaO₃SO), and a hydroxyl group. The structure includes a pyrazole ring system and a sulfonate group.</p>
314	 <p>Chemical structure of compound 314: A complex molecule featuring a central core with multiple hydroxyl groups, a sodium sulfonate group (NaO₃SO), and a hydroxyl group. The structure includes a pyrazole ring system and a sulfonate group.</p>
	 <p>Chemical structure of compound 314: A complex molecule featuring a central core with multiple hydroxyl groups, a sodium sulfonate group (NaO₃SO), and a hydroxyl group. The structure includes a pyrazole ring system and a sulfonate group.</p>

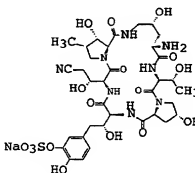
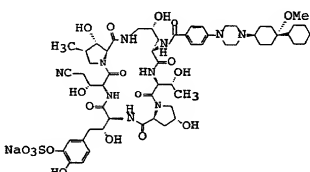
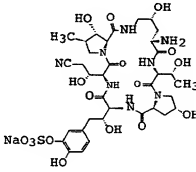
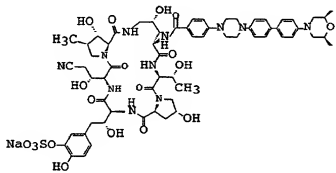
Preparation No.	Formula
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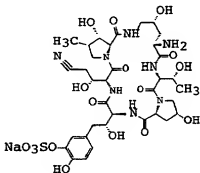
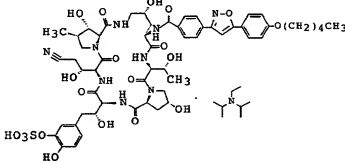
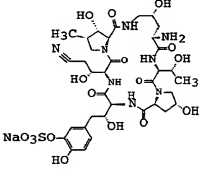
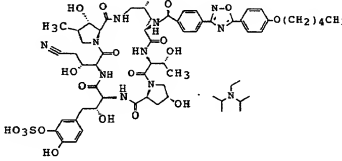
Preparation No.	Formula
317	 <p>Chemical structure of Preparation 317, top part: A complex molecule featuring a central core with multiple hydroxyl groups, a methyl group, a nitrile group, and a sodium sulfonate group (NaO₃SO) attached to a phenyl ring.</p>
	 <p>Chemical structure of Preparation 317, bottom part: A complex molecule featuring a central core with multiple hydroxyl groups, a methyl group, a nitrile group, and a sodium sulfonate group (NaO₃SO) attached to a phenyl ring. The structure is more complex than the top part, with additional functional groups and a different arrangement of the core.</p>
318	 <p>Chemical structure of Preparation 318, top part: A complex molecule featuring a central core with multiple hydroxyl groups, a methyl group, a nitrile group, and a sodium sulfonate group (NaO₃SO) attached to a phenyl ring.</p>
	 <p>Chemical structure of Preparation 318, bottom part: A complex molecule featuring a central core with multiple hydroxyl groups, a methyl group, a nitrile group, and a sodium sulfonate group (NaO₃SO) attached to a phenyl ring. The structure is more complex than the top part, with additional functional groups and a different arrangement of the core.</p>

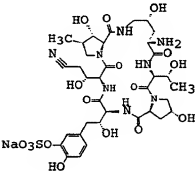
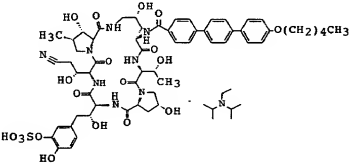
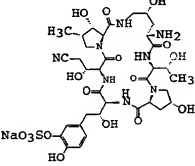
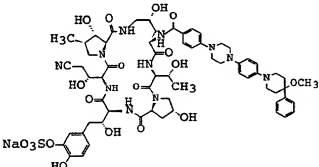
Preparation No.	Formula
319	 <p>Chemical structure of compound 319: A complex molecule featuring a central core with multiple hydroxyl groups, a methyl group, a nitrile group, and a sodium sulfonate group (NaO₃SO₃). The structure includes a benzene ring with a hydroxyl group and a sulfonate group, and a pyridine ring with a methyl group.</p>
	 <p>Chemical structure of compound 319: A complex molecule featuring a central core with multiple hydroxyl groups, a methyl group, a nitrile group, and a sodium sulfonate group (NaO₃SO₃). The structure includes a benzene ring with a hydroxyl group and a sulfonate group, and a pyridine ring with a methyl group.</p>
320	 <p>Chemical structure of compound 320: A complex molecule featuring a central core with multiple hydroxyl groups, a methyl group, a nitrile group, and a sodium sulfonate group (NaO₃SO₃). The structure includes a benzene ring with a hydroxyl group and a sulfonate group, and a pyridine ring with a methyl group.</p>
	 <p>Chemical structure of compound 320: A complex molecule featuring a central core with multiple hydroxyl groups, a methyl group, a nitrile group, and a sodium sulfonate group (NaO₃SO₃). The structure includes a benzene ring with a hydroxyl group and a sulfonate group, and a pyridine ring with a methyl group.</p>

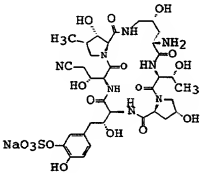
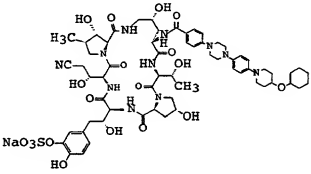
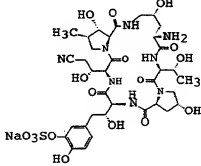
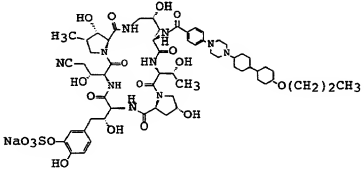
Preparation No.	Formula
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322	
	

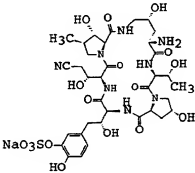
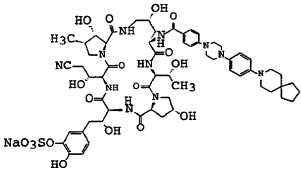
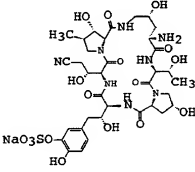
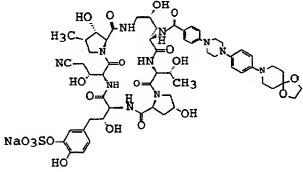
Preparation No.	Formula
323	 <p>Chemical structure of Preparation 323: A complex molecule featuring a central core with multiple hydroxyl groups, a methyl group, a nitrile group, and a sodium sulfonate group (NaO₃SO₃-) attached to a phenyl ring. The structure includes several amide and ester linkages.</p>
	 <p>Chemical structure of Preparation 323 (continued): The structure continues with a complex side chain including a morpholine ring, a methoxy group (OMe), and a sodium sulfonate group (NaO₃SO₃-) attached to a phenyl ring.</p>
324	 <p>Chemical structure of Preparation 324: A complex molecule featuring a central core with multiple hydroxyl groups, a methyl group, a nitrile group, and a sodium sulfonate group (NaO₃SO₃-) attached to a phenyl ring. The structure includes several amide and ester linkages.</p>
	 <p>Chemical structure of Preparation 324 (continued): The structure continues with a complex side chain including a morpholine ring, a thioether group (S), and a sodium sulfonate group (NaO₃SO₃-) attached to a phenyl ring.</p>

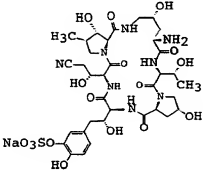
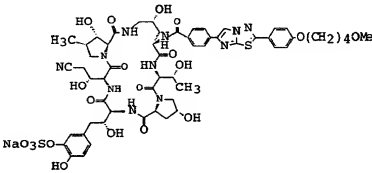
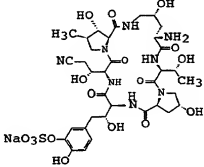
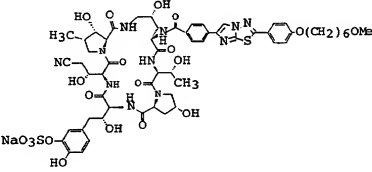
Preparation No.	Formula
325	
	
326	
	

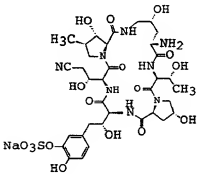
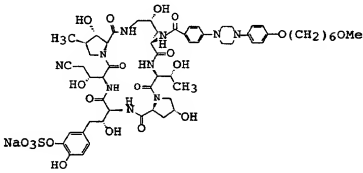
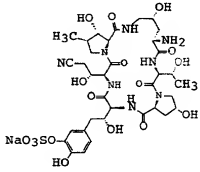
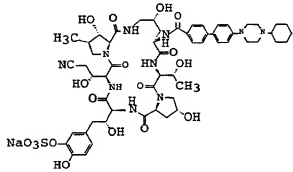
Preparation No.	Formula
327	
	
328	
	

Preparation No.	Formula
329	
	
330	
	

Preparation No.	Formula
331	
	
332	
	

Preparation No.	Formula
333	 <p>Chemical structure of Preparation 333, top part: A complex molecule featuring a central core with multiple hydroxyl groups, a nitrile group (NC), and a sodium sulfonate group (NaO₃SO₃) attached to a phenyl ring. The structure includes several amide and ester linkages, and a methyl group (H₃C).</p>
	 <p>Chemical structure of Preparation 333, bottom part: A complex molecule featuring a central core with multiple hydroxyl groups, a nitrile group (NC), and a sodium sulfonate group (NaO₃SO₃) attached to a phenyl ring. The structure includes several amide and ester linkages, a methyl group (H₃C), and a complex side chain containing a benzene ring and a cyclohexane ring.</p>
334	 <p>Chemical structure of Preparation 334, top part: A complex molecule featuring a central core with multiple hydroxyl groups, a nitrile group (NC), and a sodium sulfonate group (NaO₃SO₃) attached to a phenyl ring. The structure includes several amide and ester linkages, and a methyl group (H₃C).</p>
	 <p>Chemical structure of Preparation 334, bottom part: A complex molecule featuring a central core with multiple hydroxyl groups, a nitrile group (NC), and a sodium sulfonate group (NaO₃SO₃) attached to a phenyl ring. The structure includes several amide and ester linkages, a methyl group (H₃C), and a complex side chain containing a benzene ring and a cyclohexane ring.</p>

Preparation No.	Formula
335	 <p>Chemical structure of compound 335: A complex molecule featuring a central core with multiple hydroxyl groups, a methyl group, a nitrile group, and a sodium sulfonate group (NaO₃SO₃-) attached to a phenyl ring. The structure includes several amide and ester linkages.</p>
	 <p>Chemical structure of compound 336 (top): Similar to compound 335, but with a different side chain on the phenyl ring, specifically a (4-methoxyphenyl)thio group (O(CH₂)₄OMe).</p>
336	 <p>Chemical structure of compound 336 (bottom): Similar to compound 335, but with a different side chain on the phenyl ring, specifically a (4-methoxyphenyl)thio group (O(CH₂)₆OMe).</p>
	 <p>Chemical structure of compound 336 (bottom): Similar to compound 335, but with a different side chain on the phenyl ring, specifically a (4-methoxyphenyl)thio group (O(CH₂)₆OMe).</p>

Preparation No.	Formula
337	 <p>Chemical structure of compound 337: A complex molecule featuring a central core with multiple hydroxyl groups, a sodium sulfonate group (NaO₃SO), and a hydroxyl group. The structure includes a pyridine ring and a substituted benzene ring.</p>
	 <p>Chemical structure of compound 337: A complex molecule featuring a central core with multiple hydroxyl groups, a sodium sulfonate group (NaO₃SO), and a hydroxyl group. The structure includes a pyridine ring and a substituted benzene ring.</p>
338	 <p>Chemical structure of compound 338: A complex molecule featuring a central core with multiple hydroxyl groups, a sodium sulfonate group (NaO₃SO), and a hydroxyl group. The structure includes a pyridine ring and a substituted benzene ring.</p>
	 <p>Chemical structure of compound 338: A complex molecule featuring a central core with multiple hydroxyl groups, a sodium sulfonate group (NaO₃SO), and a hydroxyl group. The structure includes a pyridine ring and a substituted benzene ring.</p>

The following compounds [Preparations 291 to 338] were obtained according to a similar manner to that of Preparation 10.

5 Preparation 291

MASS (m/z): 1283.3 (M^+ -Na)

Preparation 292

MASS (m/z): 1338.3 (M^+ -Na)

10

Preparation 293

MASS (m/z): 1313.2 (M^+ -Na)

Preparation 294

15 MASS (m/z): 1329.3 (M^+ -Na)

Preparation 295

MASS (m/z): 1321.5 (M^+ -Na)

20 Preparation 296

The object compound was used directly in the next reaction without purification.

Preparation 297

25 MASS (m/z): 1320.4 (M^+ -Na)

Preparation 298

The object compound was used directly in the next reaction without purification.

30

Preparation 299

IR (KBr): 1605, 1444 cm^{-1}

MASS (m/z): 1372 (M -23)

Preparation 300

MASS (m/z): 1232.2 (M^+-Na)

Preparation 301

- 5 The object compound was used directly in the next reaction without purification.

Preparation 302

- 10 The object compound was used directly in the next reaction without purification.

Preparation 303

- 15 The object compound was used directly in the next reaction without purification.

Preparation 304

The object compound was used directly in the next reaction without purification.

- 20 Preparation 305

The object compound was used directly in the next reaction without purification.

Preparation 306

- 25 The object compound was used directly in the next reaction without purification.

Preparation 307

- 30 The object compound was used directly in the next reaction without purification.

Preparation 308

The object compound was used directly in the next reaction without purification.

Preparation 309

The object compound was used directly in the next reaction without purification.

5 Preparation 310

The object compound was used directly in the next reaction without purification.

Preparation 311

10 MASS (m/z): 1361 ($M^+ + 23$)

Preparation 312

MASS (m/z): 1308 ($M^+ - 23$)

15 Preparation 313

The object compound was used directly in the next reaction without purification.

Preparation 314

20 The object compound was used directly in the next reaction without purification.

Preparation 315

MASS (m/z): 1304.3 ($M^+ - Na$)

25

Preparation 316

IR (KBr): 3345.9, 1633.4, 1511.9, 1232.3 cm^{-1}

NMR (DMSO- d_6 , δ): 0.96 (3H, d, $J=6.8\text{Hz}$), 1.08 (3H, d, $J=6.1\text{Hz}$), 1.23-1.26 (2H, m), 2.80-5.21 (51H, m),

30

6.66-8.72 (20H, m)

MASS (m/z): 1372.3 ($M^+ - Na$)

Preparation 317

IR (KBr): 3336.2, 1631.5, 1510.0, 1230.4 cm^{-1}

35

NMR (DMSO- d_6 , δ): 0.95 (3H, d, $J=7.1\text{Hz}$), 1.08 (3H, d,

J=5.8Hz), 1.24-5.21 (50H, m), 6.68-8.72 (22H, m)
MASS (m/z): 1308.4 (M^+ -Na)

Preparation 318

5 MASS (m/z): 1262(M^+ -23)

Preparation 319

MASS (m/z): 1262(M^+ -23)

10 Preparation 320

The object compound was used directly in the next reaction without purification.

Preparation 321

15 The object compound was used directly in the next reaction without purification.

Preparation 322

20 The object compound was used directly in the next reaction without purification.

Preparation 323

The object compound was used directly in the next reaction without purification.

25

Preparation 324

The object compound was used directly in the next reaction without purification.

30 Preparation 325

The object compound was used directly in the next reaction without purification.

Preparation 326

35 The object compound was used directly in the next

reaction without purification.

Preparation 327

- 5 The object compound was used directly in the next reaction without purification.

Preparation 328

- 10 The object compound was used directly in the next reaction without purification.

Preparation 329

The object compound was used directly in the next reaction without purification.

15 Preparation 330

IR (KBr): 3351.7, 2256.3, 1633.4, 1232.3, 1116.6 cm^{-1}

NMR (DMSO- d_6 , δ): 0.96 (3H, d, $J=6.7\text{Hz}$), 1.08 (3H, d, $J=5.9\text{Hz}$), 1.80-5.20 (52H, m), 5.91-5.94 (1H, m), 6.68-8.72 (21H, m)

- 20 MASS (m/z): 1338.4 ($M^+-\text{Na}$)

Preparation 331

IR (KBr): 2256.3, 1633.4, 1510.0, 1085.7 cm^{-1}

NMR (DMSO- d_6 , δ): 0.94-5.93 (68H, m), 6.69-8.72 (16H, m)

- 25 MASS (m/z): 1330.5 ($M^+-\text{Na}$)

Preparation 332

IR (KBr): 3351.7, 2256.3, 1666.2, 1633.4, 1230.4 cm^{-1}

NMR (DMSO- d_6 , δ): 0.81-5.20 (74H, m), 5.88-5.91 (1H, m), 6.68-8.72 (12H, m)

30

Preparation 333

IR (KBr): 2256.3, 1633.4, 1510.0, 1322.9, 1232.3 cm^{-1}

NMR (DMSO- d_6 , δ): 0.96 (3H, d, $J=6.7\text{Hz}$), 1.09 (3H, d, $J=5.6\text{Hz}$), 1.24-5.20 (57H, m), 5.89-5.93 (1H, m),

35

6.68-8.79 (16H, m)

MASS (m/z): 1286.3 (M^+ -Na)

Preparation 334

- 5 IR (KBr): 3349.7, 2256.3, 1633.4, 1232.3 cm^{-1}
NMR (DMSO- d_6 , δ): 0.96 (3H, d, $J=6.7\text{Hz}$), 1.08 (3H, d, $J=5.5\text{Hz}$), 1.70-5.21 (53H, m), 5.90-5.93 (1H, m), 6.68-8.72 (16H, m)
MASS (m/z): 1336.3 (M^+ +Na)

10

Preparation 335

- 15 NMR (DMSO- d_6 , δ): 0.96 (3H, d, $J=6.7\text{Hz}$), 1.10 (3H, d, $J=5.7\text{Hz}$), 1.6-2.0 (8H, m), 2.2-2.5 (3H, m), 2.7 (1H, m), 2.9 (2H, m), 3.23 (3H, s), 3.34 (2H, m), 3.74 (2H, m), 3.6-4.6 (15H, m), 4.85 (3H, m), 5.03 (1H, d, $J=6.2\text{Hz}$), 5.10 (1H, m), 5.20 (2H, m), 5.88 (1H, m), 6.71 (1H, d, $J=8.2\text{Hz}$), 6.78 (1H, d, $J=8.2\text{Hz}$), 6.98 (1H, s), 7.14 (2H, d, $J=8.9\text{Hz}$), 7.42 (1H, d, $J=8.3\text{Hz}$), 7.51 (1H, d, $J=9.3\text{Hz}$), 7.79 (1H, m), 7.90 (2H, d, $J=8.9\text{Hz}$), 7.97 (4H, s), 8.32 (1H, d, $J=7.7\text{Hz}$), 8.51 (1H, d, $J=7.5\text{Hz}$), 8.71 (1H, m), 8.84 (1H, s)
MASS (m/z): 1290.3 (M^+ +Na)

20

25 Preparation 336

MASS (m/z): 1318.3 (M^+ -Na)

Preparation 337

MASS (m/z): 1279.4 (M^+ -Na)

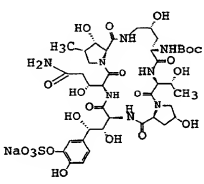
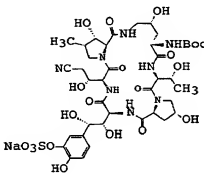
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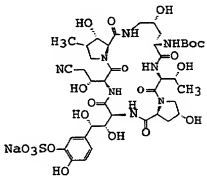
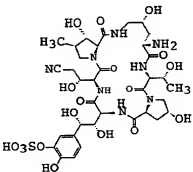
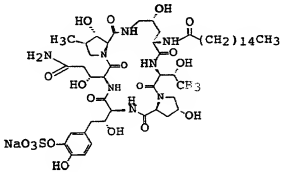
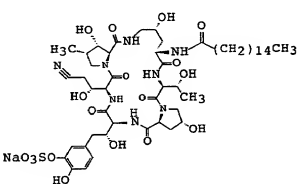
Preparation 338

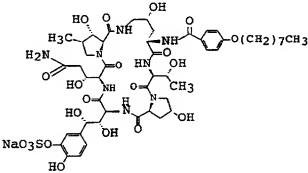
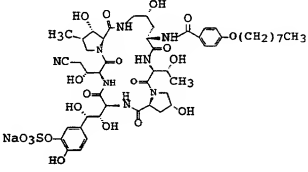
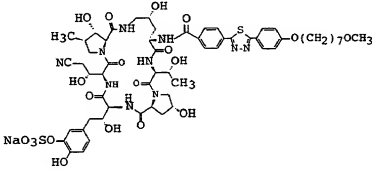
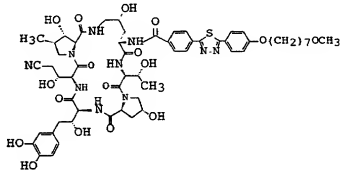
MASS (m/z): 1231.4 (M^+ -Na)

35

The Starting Compounds (339) to (343) used and the Object Compounds (339) to (343) obtained in the following Preparations 339 to 343 are given in the table as below, in which the formulas of the starting compounds are in the upper column and the formulas of the object compounds are in the lower column, respectively.

Preparation No.	Formula
339	
	

Preparation No.	Formula
340	
	
341	
	

Preparation No.	Formula
342	
	
343	
	

The following compound was obtained according to a similar manner to that of Preparation 2.

5

Preparation 339

IR (KBr): 1666, 1633, 1516, 1443, 1279, 1254 cm^{-1}

NMR (DMSO- d_6 +D₂O, δ): 0.94 (3H, d, J=6.74Hz), 1.09 (3H, d, J=5.59Hz), 1.36 (9H, s), 1.50-2.00 (3H, m), 2.10-2.40 (3H, m), 2.55-3.40 (5H, m), 3.55-4.50 (12H, m), 4.70-4.90 (2H, m), 6.73 (1H, d, J=8.20Hz), 6.82 (1H, d, J=9.80Hz), 7.06 (1H, s)

ESI MASS (m/z)(Positive): 1047.2 (M^+ +Na)

Elemental Analysis Calcd. for $\text{C}_{40}\text{H}_{57}\text{N}_8\text{O}_{20}\text{SNa}\cdot 5\text{H}_2\text{O}$:

15

C 43.09, H 6.06, N 10.05

Found: C 43.05, H 6.09, N 9.98

HPLC (20% CH_3CN -pH 6.86 standard buffer solution; YMC-ODS 150x4.6mm): LT 5.38 min.

20

The following compound was obtained according to a similar manner to that of Preparation 9.

Preparation 340

NMR (DMSO- d_6 +D₂O, δ): 0.94 (3H, d, J=6.74Hz), 1.14 (3H, d, J=5.89Hz), 1.30-1.55 (1H, m), 1.70-2.00 (1H, m), 2.05-2.45 (3H, m), 2.50-2.90 (3H, m), 3.05-3.35 (1H, m), 3.50-4.50 (16H, m), 4.65-4.95 (2H, m), 6.70-6.85 (2H, m), 7.09 (1H, d, J=1.56Hz)

ESI MASS (m/z)(Positive): 925.2 (M^+)

30

HPLC (20% CH_3CN -pH 6.86 standard buffer solution; YMC-ODS 150x4.6mm): LT 2.01 min.

The following compounds [Preparation 341 to 342] were obtained according to a similar manner to that of Preparation

35 2.

Preparation 341

IR (KBr): 3354, 2925.5, 2854, 2256, 1631.5, 1535, 1516,
1448, 1267, 1246, 1084, 1047 cm^{-1}

5 MASS (m/z): 1123.5 ($\text{M}^+ - \text{Na}$)

Elemental Analysis Calcd. for $\text{C}_{51}\text{H}_{79}\text{N}_8\text{O}_{18}\text{SNa} \cdot 7\text{H}_2\text{O}$:

C 48.10, H 7.36, N 8.80

Found: C 48.31, H 7.26, N 8.72

10 The following compound was obtained according to a
similar manner to that of Preparation 2.

Preparation 342

IR (KBr): 2931, 1659, 1635, 1531, 1506, 1439, 1387,
15 1350 cm^{-1}

MASS (m/z): 1133.4 ($\text{M}^+ - \text{Na}$)

Preparation 343

To a solution of Starting Compound (343) (1 g) in
20 trifluoroacetic acid (20 ml) was added 1N HCl aq. (4 ml) and
stirred for 7 hours at ambient temperature. The reaction
mixture was pulverized with water (90 ml). The precipitate
was collected by filtration and dried under reduced pressure.

The powder was added to 36% acetonitrile aq. (190 ml) and
25 subjected to column chromatography on ODS (YMC-gel ODS-AM X
S-50) (Trademark: prepared by Yamamura Chemical Lab.) and
eluted with 35% acetonitrile aq. The fractions containing
the object compound were combined and evaporated under
reduced pressure to remove acetonitrile. The residue was
30 lyophilized to give Object Compound (343) (319 mg).

IR (KBr): 3344.0, 2254, 1658.5, 1635.3, 1444.4,
1257.4 cm^{-1}

ESI-MASS (m/z): 1213 ($\text{M}^+ - 1$)

Preparation 344

Dimethylformamide (485 /), p-pentyloxyacetophenone (30.3 kg) and dimethyl terephthalate (45.6 kg) were charged in 2000-liter reactor and stirred. To this mixture was added
5 potassium tert-butoxide (24.7 kg) in several portions and, after that, a reaction was carried out at the inner temperature of 20 to 25°C for 3.5 hours. After completion of the reaction, methanol (1210 /) was added to the reaction solution at 20 to 30°C and then 6N hydrochloric acid (49 /) at
10 5 to 15°C. The mixture was stirred at room temperature for 1 hour, and the resulting appeared crystals were filtered and washed with methanol (152 /) and then water (152 /). The crystals were dried overnight in vacuo to give 1-(4-methoxycarbonylphenyl)-3-(4-pentyloxyphenyl)propane-1,3-dione
15 (49.6 kg).

NMR (CDCl₃, δ): 0.95 (3H, t, J=1.4Hz), 1.30-1.60 (4H, m), 1.76-1.89 (2H, m), 3.95 (3H, s), 4.03 (2H, t, J=1.3Hz), 6.84 (1H, s), 6.98 (2H, d, J=1.4Hz), 7.99 (2H, d, J=1.4Hz), 8.01 (2H, d, J=1.7Hz), 8.13 (2H, d, J=1.7Hz)
20

MASS (m/z): 369 (M⁺+1)

Preparation 345

Dimethylformamide (123 /), 1-(4-methoxycarbonylphenyl)-3-(4-pentyloxyphenyl)propane-1,3-dione (24.5 kg) and ammonium formate (21.0 kg) were charged in 2000-liter reactor at room temperature and heated, and a reaction was carried out at the inner temperature of 100 to 105°C for 5 hours. After
30 completion of the reaction, the mixture was cooled down to room temperature, ethyl acetate (613 /) and water (613 /) were added, the mixture was stirred, and an ethyl acetate layer was separated, and then washed with 10% sodium chloride solution (613 /) and with 20% sodium chloride solution (613 /). The ethyl acetate layer was concentrated in vacuo to 125
35 / and then diluted with n-heptane (625 /) at the inner

temperature of 40 to 45°C to separate crystals of 1-amino-1-(4-methoxycarbonylphenyl)-3-oxo-3-(4-pentyloxyphenyl)-1-propene. The crystals were filtered at room temperature and washed with a mixture of n-heptane (104 l) and ethyl acetate (21 l). The crystals were dried overnight in vacuo and purified by suspending in a 70% aqueous acetone (158 l) to give 1-amino-1-(4-methoxycarbonylphenyl)-3-oxo-3-(4-pentyloxyphenyl)-1-propene (14.3 kg).

NMR (CDCl₃, δ): 0.94 (3H, t, J=1.4Hz), 1.30-1.55 (4H, m), 1.70-1.90 (2H, m), 3.96 (3H, s), 4.01 (2H, t, J=1.3Hz), 6.13 (1H, br s), 6.92 (2H, d, J=1.8Hz), 7.70 (2H, d, J=1.7Hz), 7.92 (2H, d, J=1.8Hz), 8.13 (2H, d, J=1.7Hz)

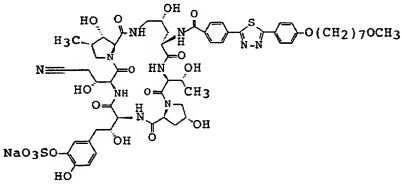
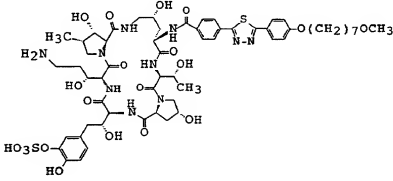
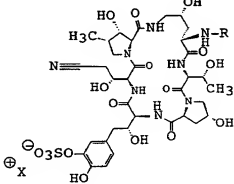
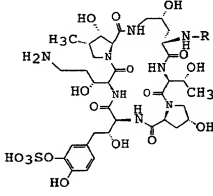
MASS (m/z): 368 (M⁺+1)

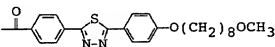
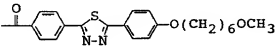
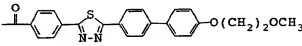
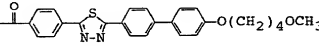
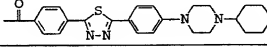

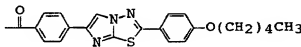

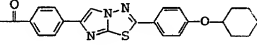
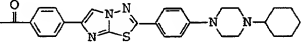
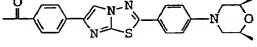
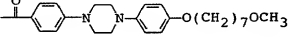

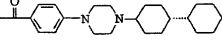
to be continued on the next page

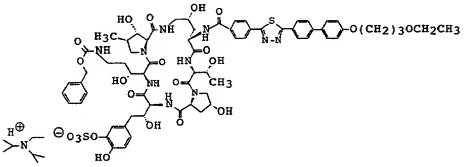
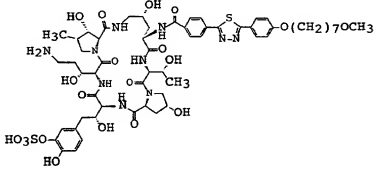
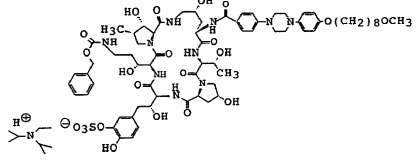
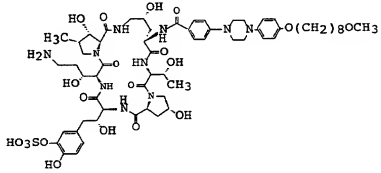
The Starting Compounds used and the Object Compounds obtained in the following Examples 1 to 17 are given in the table as below, in which the formulas of the starting compounds are in the upper column and the formulas of the

5 object compounds are in the lower column, respectively.

Example No.	Formula
1	

Example No.	Formula
2	
	
3 (13	
	

Example No.	R	X
3		Na
4		Na
5		Na
6		Na
7		
8		
9		Na
10		Na
11		Na
12		
13		Na

Example No.	Formula
16	
	
17	
	

Example 1

- A solution of crude Starting compound (5.6 g) in methanol (168 ml) - water (336 ml) was treated with cobalt chloride hexahydrate (3.08 g) and the mixture stirred to give a pink colored solution. Sodium borohydride (2.46 g) was then added portionwise over 1 hour. Additional cobalt chloride (1.54 g) was added followed by sodium borohydride (1.23 g, portionwise). After a total reaction time of 2 hours 50% aqueous acetonitrile (600 ml) was added and insoluble material removed by filtration. The filtrate was evaporated to remove organic solvent and sufficient 1N-sodium hydroxide was added to the remaining aqueous layer to effect solution. This clear aqueous solution was then purified by ODS column chromatography eluting with aqueous acetonitrile. Object compounds-containing fractions were pooled, evaporated, and lyophilized to give Object compound (1.4 g) as an amorphous white powder.

IR (KBr): 1658.5, 1635.3, 1546.6, 1529.3, 1517.7,
1444.4, 1257.4 cm^{-1}

- NMR (DMSO- d_6 , δ): 0.96 (3H, d, $J=6.8\text{Hz}$), 1.10 (3H, d, $J=6\text{Hz}$), 1.30-1.60 (8H, m), 1.60-2.50 (15H, m), 3.21 (3H, s), 2.80-5.40 (29H, m), 6.74 (1H, d, $J=8.2\text{Hz}$), 6.80-6.85 (1H, m), 7.07 (1H, br s), 7.14 (2H, d, $J=8.9\text{Hz}$), 7.40-7.80 (4H, m), 7.97 (2H, d, $J=8.8\text{Hz}$), 8.09 (4H, ABq like, br m), 8.20-8.30 (1H, m), 8.80-8.90 (1H, m)

MASS (m/z): 1313.3 (M^+-1)

Elemental Analysis Calcd. for $\text{C}_{58}\text{H}_{78}\text{N}_{10}\text{O}_{21}\text{S}_2\cdot 9\text{H}_2\text{O}$:

C 47.34, H 6.16, N 9.52

- Found: C 47.42, H 6.26, N 9.47

The following compounds [Examples 2 to 13] were obtained according to a similar manner to that of Example 1.

35 Example 2

IR (KBr): 1648.8, 1631.5, 1538.9, 1515.8, 1442.5,
1257.4 cm^{-1}

NMR (DMSO- d_6 , δ): 0.98 (3H, d, $J=6.7\text{Hz}$), 1.24 (3H, d,
 $J=5.6\text{Hz}$), 1.40-1.60 (8H, m), 1.60-2.65 (15H, m),
2.80-5.50 (27H, m), 3.21 (3H, s), 3.30 (2H, t,
 $J=6.3\text{Hz}$), 6.72 (1H, d, $J=8.1\text{Hz}$), 6.78 (1H, dd,
 $J=1.6$ and 8.3Hz), 7.00 (1H, d, $J=1.6\text{Hz}$), 7.13 (2H,
d, $J=8.9\text{Hz}$), 7.46 (1H, d, $J=8.1\text{Hz}$), 7.60-7.90 (2H,
m), 7.97 (2H, d, $J=8.7\text{Hz}$), 8.04-8.14 (4H, m), 8.24-
8.27 (1H, m), 8.70-9.00 (2H, m)

MASS (m/z): 1297.3 (M^+-1)

Elemental Analysis Calcd. for $\text{C}_{58}\text{H}_{78}\text{N}_{10}\text{O}_{20}\text{S}_2 \cdot 7.5\text{H}_2\text{O}$:

C 48.56, H 6.53, N 9.76

Found: C 48.56, H 6.31, N 9.63

Example 3

IR (KBr): 1633.4, 1517.7, 1444.4, 1257.4 cm^{-1}

NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.8\text{Hz}$), 1.13 (3H, d,
 $J=5.7\text{Hz}$), 1.20-1.65 (10H, m), 1.65-2.65 (15H, m),
2.70-5.50 (27H, m), 3.21 (3H, s), 4.07 (2H, t,
 $J=6.5\text{Hz}$), 6.71 (1H, d, $J=8\text{Hz}$), 6.75-6.80 (1H, m),
6.98 (1H, d, $J=1.6\text{Hz}$), 7.13 (2H, d, $J=8.9\text{Hz}$), 7.46
(1H, d, $J=8\text{Hz}$), 7.55-7.85 (2H, m), 7.97 (2H, d,
 $J=8.8\text{Hz}$), 8.07 (4H, ABq, $J=10.8\text{Hz}$), 8.09-8.13 (1H,
m), 8.79 (1H, d, $J=7.9\text{Hz}$), 8.55-9.00 (1H, br s)

MASS (m/z): 1311.3 (M^+-1)

Elemental Analysis Calcd. for $\text{C}_{59}\text{H}_{80}\text{N}_{10}\text{O}_{20}\text{S}_2 \cdot 10\text{H}_2\text{O}$:

C 47.45, H 6.75, N 9.38

Found: C 47.68, H 6.27, N 9.21

Example 4

IR (KBr): 1648.8, 1631.5, 1540.8, 1513.8, 1452.1 cm^{-1}

NMR (DMSO- d_6 , δ): 0.95 (3H, d, $J=6.6\text{Hz}$), 1.07 (3H, d,
 $J=6\text{Hz}$), 1.1-2.7 (21H, m), 2.7-5.5 (32H, m), 6.68-
6.74 (2H, m), 6.9-6.94 (1H, m), 7.13 (2H, d,

J=8.9Hz), 7.2-7.5 (1H, m), 7.5-7.8 (2H, m), 7.97
(2H, d, J=8.8Hz), 8.09 (4H, s), 8.29 (1H, d,
J=7.3Hz), 8.5-8.9 (2H, m)

MASS (m/z): 1283.3 ($M^{+}-1$)

5

Example 5

IR (KBr): 1635.3, 1531.2, 1444.4, 1251.6 cm^{-1}

NMR (DMSO- d_6 , δ): 0.96 (3H, d, J=6.7Hz), 1.14 (3H, d,
J=6Hz), 1.40-5.30 (41H, m), 3.67-3.70 (2H, m),
4.15-4.23 (2H, m), 6.66 (1H, d, J=8Hz), 6.64-6.72
(1H, m), 6.96 (1H, br s), 7.09 (2H, d, J=8.9Hz),
7.4-7.8 (4H, m), 7.57 (2H, d, J=6.3Hz), 7.74 (2H,
d, J=8.8Hz), 8.0-8.3 (7H, m), 8.73 (1H, d, J=7.5Hz)

MASS (m/z): 1304.3 (M^{+})

15

Elemental Analysis Calcd. for $\text{C}_{59}\text{H}_{72}\text{N}_{10}\text{O}_{20}\text{S}_2 \cdot 11\text{H}_2\text{O}$:

C 47.13, H 6.30, N 9.32

Found: C 47.22, H 5.90, N 8.82

Example 6

20

IR (KBr): 1635.3, 1531.2, 1508.1, 1444.4, 1251.6 cm^{-1}

NMR (DMSO- d_6 , δ): 0.97 (3H, d, J=6.7Hz), 1.14 (3H, d,
J=5.4Hz), 1.3-5.3 (44H, m), 3.25 (3H, s), 4.05 (2H,
t, J=6Hz), 6.70 (1H, d, J=8.2Hz), 6.75-6.79 (1H,
m), 6.96 (1H, br s), 7.07 (2H, d, J=8.9Hz), 7.4-7.8
(4H, m), 7.73 (2H, d, J=8.8Hz), 7.87 (2H, d,
J=8.5Hz), 8.08-8.16 (7H, m), 8.7-8.8 (1H, m)

25

MASS (m/z): 1332.4 (M^{+})

Elemental Analysis Calcd. for $\text{C}_{61}\text{H}_{76}\text{N}_{10}\text{O}_{20}\text{S}_2 \cdot 11\text{H}_2\text{O}$:

C 47.84, H 6.45, N 9.15

30

Found: C 48.10, H 6.00, N 8.94

Example 7

IR (KBr): 1635.3, 1606.4, 1531.2, 1496.5, 1444.4,
1419.4 cm^{-1}

35

NMR (DMSO- d_6 , δ): 0.97 (3H, d, J=6.8Hz), 1.11 (3H, d,

J=5.7Hz), 1.05-1.04 (5H, m), 1.50-5.30 (52H, complex m), 6.67 (1H, d, J=5.7Hz), 6.73-6.80 (1H, m), 7.01 (1H, d, J=1.6Hz), 7.08 (2H, d, J=9Hz), 7.4-7.8 (3H, m), 7.85 (2H, d, J=8.7Hz), 8.07 (4H, ABq, J=9Hz), 8.31 (1H, d, J=6.9Hz), 8.71 (1H, s), 8.91 (1H, d, J=7.4Hz)

MASS (m/z): 1319.4 (M^+-1)

Elemental Analysis Calcd. for $C_{60}H_{80}N_{12}O_{18}S_2 \cdot 9H_2O$:

C 48.57, H 6.66, N 11.33

Found: C 48.77, H 6.54, N 11.25

Example 8

IR (KBr): 1635.3, 1529.3, 1519.6, 1467.6, 1446.4, 1257.4 cm^{-1}

NMR (DMSO- d_6 , δ): 0.91 (3H, t, J=7Hz), 0.96 (3H, d, J=8.3Hz), 1.12 (3H, d, J=5.6Hz), 1.2-2.6 (17H, m), 2.6-5.4 (29H, m), 6.71 (1H, d, J=8Hz), 6.77 (1H, br d, J=8Hz), 6.98 (1H, d, J=1.7Hz), 7.14 (2H, d, J=8.9Hz), 7.45 (1H, d, J=8.5Hz), 7.4-7.8 (3H, m), 7.90 (2H, d, J=8.8Hz), 8.05 (4H, s), 8.1-8.3 (1H, s), 8.64 (1H, d, J=6.9Hz), 8.85 (1H, s)

MASS (m/z): 1278.3 (M^+-1)

Elemental Analysis Calcd. for $C_{57}H_{73}N_{11}O_{19}S_2 \cdot 9H_2O$:

C 47.46, H 6.36, N 10.68

Found: C 47.58, H 6.17, N 10.62

Example 9

IR (KBr): 3361.3, 2937.1, 1635.3, 1523.5, 1461.8, 1251.6 cm^{-1}

NMR (DMSO- d_6 , δ): 0.97 (3H, d, J=6.8Hz), 1.10 (3H, d, J=5.9Hz), 1.2-5.3 (49H, m), 6.67-6.80 (2H, m), 7.01 (1H, d, J=1.6Hz), 7.15 (2H, d, J=9Hz), 7.4-7.8 (3H, m), 7.88 (2H, d, J=8.8Hz), 7.96 (4H, s), 8.35 (1H, d, J=8.3Hz), 8.7-8.8 (2H, m), 8.86 (1H, s)

API-ES MASS (Negative): 1290.3 (M^+-1)

Elemental Analysis Calcd. for $C_{58}H_{73}N_{11}O_{19}S_2 \cdot 8H_2O$:

C 48.29 H 6.26, N 10.53

Found: C 48.49 H 6.24, N 10.73

5 Example 10

IR (KBr): 1637.3, 1523.5, 1459.9, 1238.1 cm^{-1}

MASS (m/z): 1358.4 ($M^{+}-1$)

Example 11

10 IR (KBr): 3357.5, 1631.5, 1517.7, 1465.6, 1450.2,
1241.9 cm^{-1}

NMR (DMSO- d_6 , δ): 0.98 (3H, d, $J=6.8Hz$), 1.10 (3H, d,
 $J=6Hz$), 1.18 (6H, d, $J=6Hz$), 1.5-2.7 (11H, m), 2.8-
5.4 (33H, m), 6.71 (1H, d, $J=8.2Hz$), 6.78 (1H, dd,
15 $J=8$ and 1.6Hz), 7.01 (1H, d, $J=1.6Hz$), 7.12 (2H, d,
 $J=9Hz$), 7.44 (1H, d, $J=8.7Hz$), 7.6-7.9 (1H, m),
7.67 (1H, d, $J=8Hz$), 7.78 (2H, d, $J=8.8Hz$), 7.96
(4H, s), 8.35 (1H, d, $J=7Hz$), 7.6-8.8 (1H, br s),
8.75 (1H, d, $J=7Hz$), 8.81 (1H, s)

20 API-ES MASS (Negative): 1305.3 ($M^{+}-1$)

Elemental Analysis Calcd. for $C_{58}H_{74}N_{12}O_{19}S_2 \cdot 8H_2O$:

C 48.05, H 6.24, N 11.55

Found: C 47.99, H 6.25, N 11.58

25 Example 12

IR (KBr): 1631.5, 1510.0, 1446.4, 1234.2 cm^{-1}

NMR (DMSO- d_6 , δ): 0.96 (3H, d, $J=6.7Hz$), 1.09 (3H, d,
 $J=5.8Hz$), 1.2-2.65 (15H, m), 2.7-5.3 (41H, m), 3.21
(3H, s), 3.30 (2H, t, $J=6.4Hz$), 3.85 (2H, t,
30 $J=6.5Hz$), 6.70 (1H, d, $J=8.2Hz$), 6.74-6.80 (1H, m),
6.83 (2H, d, $J=9Hz$), 6.94 (2H, d, $J=9Hz$), 6.99 (1H,
s), 7.01 (2H, d, $J=8.8Hz$), 7.44 (1H, d, $J=8.6Hz$),
7.6-7.9 (2H, m), 7.80 (2H, d, $J=8.7Hz$), 8.1-8.3
(2H, m), 8.37 (1H, d, $J=7.7Hz$)

35 MASS (m/z): 1297.5 ($M^{+}-Na$)

Elemental Analysis Calcd. for $C_{60}H_{86}N_{10}O_{20}S \cdot 7H_2O$:

C 50.55, H 7.07, N 9.83

Found: C 50.68, H 7.08, N 9.82

5 Example 13

IR (KBr): 1648.8, 1631.5, 1540.8, 1511.9, 1454.1,
1238.1 cm^{-1}

NMR (DMSO- d_6 , δ): 0.8-1.3 (18H, m), 1.5-2.5 (24H, m),
2.61 (4H, br s), 2.8-5.4 (27H, m), 6.70 (1H, d,
J=8.1Hz), 6.77 (1H, br d, J=10Hz), 6.92 (2H, d,
J=9Hz), 7.00 (1H, d, J=1.6Hz), 7.42 (1H, d,
J=8.6Hz), 7.5-7.7 (2H, m), 7.76 (2H, d, J=8.6Hz),
8.30 (1H, d, J=7.1Hz), 8.44 (1H, d, J=6.9Hz), 8.46-
9.00 (1H, br s)

15 MASS (m/z): 1241.3 (M^+-1)

Elemental Analysis Calcd. for $C_{58}H_{86}N_{10}O_{18}S \cdot 10H_2O$:

C 48.94, H 7.50, N 9.84

Found: C 49.19, H 7.33, N 9.73

20 Example 14

A solution of Starting compound (150 mg) in N,N-dimethylformamide (1.5 ml) was treated with diisopropylethylamine (166.5 mg) and ethyl formimidate hydrochloride (64.8 mg) and stirred 2 days at room
25 temperature. Additional ethyl formimidate hydrochloride (39 mg) was added and stirring continued a further 3 hours 15 minutes. The reaction mixture was diluted with water and purified by ODS column chromatography, eluting with aqueous acetonitrile. Product-containing fractions were pooled,
30 evaporated, and lyophilized to give Object compound as an amorphous white powder.

IR (KBr): 1658.5, 1635.3, 1444.4, 1257.4 cm^{-1}

NMR (DMSO- d_6 , δ): 0.97 (3H, d, J=6.7Hz), 1.10 (3H, d,
J=6.1Hz), 1.20-1.60 (8H, m), 1.60-2.50 (15H, m),
35 3.21 (3H, s), 2.80-5.30 (27H, m), 6.71 (1H, d,

J=8.1Hz), 6.78 (1H, d, J=6Hz), 7.00 (1H, br s),
7.14 (2H, d, J=8.9Hz), 7.40-7.84 (4H, m), 7.84 (1H,
s), 7.97 (2H, d, J=8.8Hz), 8.08 (4H, ABq, J=8.9Hz),
8.30-8.40 (2H, m), 8.90-9.10 (2H, m)

5 MASS (m/z): 1325.4 ($M^{+}-1$)

Elemental Analysis Calcd. for $C_{58}H_{79}N_{11}O_{19}S_2 \cdot 8H_2O$:

C 48.29, H 6.64, N 10.68

Found: C 48.01, H 6.34, N 10.38

10 The following compounds [Examples 15 to 17] were
obtained according to a similar manner to that of Example 14.

Example 15

IR (KBr): 1658, 1635, 1628, 1444, 1257 cm^{-1}

15 NMR (DMSO- d_6 , δ): 0.97 (3H, d, J=6.7Hz), 1.11 (3H, d,
J=6.1Hz), 1.25-1.60 (8H, m), 1.60-2.50 (15H, m),
2.05 (3H, s), 3.21 (3H, s), 2.80-5.30 (27H, m),
6.71 (1H, d, J=8.1Hz), 6.77 (1H, d, J=8Hz), 7.00
(1H, br s), 7.13 (2H, d, J=8.9Hz), 7.30-7.90 (4H,
20 m), 7.97 (2H, d, J=8.7Hz), 8.08 (4H, ABq, J=8.8Hz),
8.50-9.00 (4H, m)

MASS (m/z): 1362.3 ($M^{+}-Na$)

Elemental Analysis Calcd. for $C_{59}H_{81}N_{11}O_{19}S_2 \cdot 9H_2O$:

C 48.06, H 6.77, N 10.45

25 Found: C 48.02, H 6.48, N 10.11

Example 16

IR (KBr): 1643.1, 1633.4, 1535.1, 1513.8, 1442.5,
1249.6 cm^{-1}

30 NMR (DMSO- d_6 , δ): 0.97 (3H, d, J=6.8Hz), 1.1-1.16 (3H,

5 m), 1.12 (3H, t, J=7Hz), 1.4-2.6 (12H, m), 2.8-5.2 (34H, m), 6.71 (1H, d, J=8Hz), 6.78 (1H, dd, J=8 and 2Hz), 7.00 (1H, d, J=2Hz), 7.08 (2H, d, J=8.8Hz), 7.45 (1H, d, J=8.9Hz), 7.6-7.8 (2H, m), 7.73 (2H, d, J=8.8Hz), 7.87 (2H, d, J=8.5Hz), 8.0-8.2 (6H, m), 8.28 (1H, d, J=7Hz), 8.91 (1H, d, J=7.6Hz), 8.5-9.05 (1H, br s)

MASS (m/z): 1331.2 (M^+-1)

Elemental Analysis Calcd. for $C_{61}H_{76}N_{10}O_{20}S_2 \cdot 10H_2O$:

10 C 48.41, H 6.39, N 9.25
Found: C 48.63, H 6.13, N 9.13

Example 17

IR (KBr): 1631.5, 1537.0, 1510.0, 1448.3, 1234.2 cm^{-1}

15 NMR (DMSO- d_6 + D_2O , δ): 0.96 (3H, d, J=6.7Hz), 1.05-1.15 (3H, m), 1.2-3.0 (33H, m), 3.15 (3H, s), 3.29 (2H, t, J=6.4Hz), 3.88 (2H, t, J=6.4Hz), 3.6-4.5 (14H, m), 4.7-4.85 (2H, m), 6.73-7.04 (9H, m), 7.75-7.9 (2H, m)

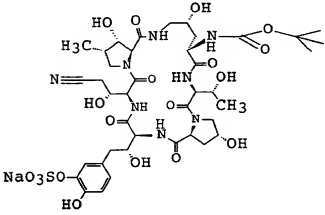
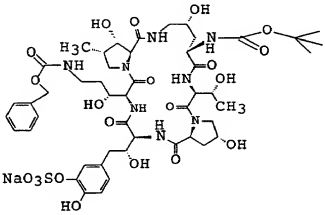
20 MASS (m/z): 1311.4 (M^+-1)

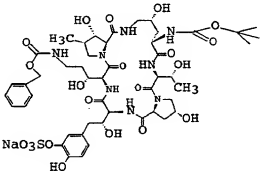
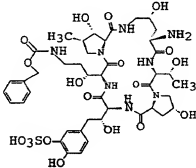
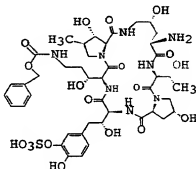
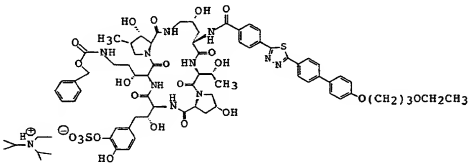
Elemental Analysis Calcd. for $C_{61}H_{88}N_{10}O_{20}S \cdot 10H_2O$:

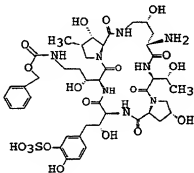
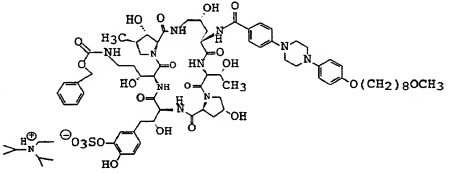
C 49.05, H 7.29, N 9.38
Found: C 48.78, H 6.83, N 9.27

25 The Starting Compounds (18) to (21) used and the Object Compounds (18) to (21) obtained in the following Examples 18 to 21 are given in the table as below, in which the formulas of the starting compounds are in the upper column and the formulas of the object compounds are in the lower column,
30 respectively.

5

Example No.	Formula
18	
	

Example No.	Formula
19	
	
20	
	

Example No.	Formula
21	
	

Example 18

- A solution of Starting compound (2.0 g) in methanol (100 ml) - water (20 ml) was treated with cobalt(II) chloride hexahydrate (1.89 g) and then stirred to give a pink solution. Sodium borohydride (1.5 g) was then added portionwise and then stirred for 1 hour at room temperature. The reaction mixture was filtered through a bed of celite, washing with methanol (100 ml) - water (30 ml) solution. The ice-cooled filtrate was then treated dropwise with a solution of benzyloxy carbonyl chloride (Z-chloride) (0.34 ml) in tetrahydrofuran (5 ml) and stirred for 1 hour at the same temperature. Ethyl acetate (50 ml) was added followed by water (200 ml) and after stirring - 5 minutes, the separated organic layer was discarded. The aqueous layer was adjusted to pH 8.8 and evaporated to remove organic solvent and then purified by ODS column chromatography, eluting with aqueous

acetonitrile (10-30%). Object compound containing fractions were pooled, evaporated, and lyophilized to give Object compound (1.61 g) as an amorphous white powder.

IR (KBr): 1666.2, 1631.5, 1517.7, 1444.4, 1267.0 cm^{-1}

5 NMR (DMSO- d_6 , δ): 0.94 (3H, d, $J=6.7\text{Hz}$), 1.00-1.15 (3H, m), 1.33 (9H, s), 1.35-2.10 (6H, m), 2.10-2.50 (4H, m), 2.80-3.30 (4H, m), 3.60-4.55 (12H, m), 4.60-4.90 (2H, m), 4.99 (2H, s), 4.50-5.30 (4H, m), 6.60-7.10 (4H, m), 7.33 (5H, s), 7.35-7.90 (3H, m), 10 8.72 (1H, br s)

MASS (m/z): 1123.3 ($\text{M}^+ - \text{Na}$)

Elemental Analysis Calcd. for $\text{C}_{48}\text{H}_{67}\text{N}_8\text{O}_{21}\text{SNa} \cdot 6\text{H}_2\text{O}$:

C 45.93, H 6.34, N 8.93

Found: C 45.68, H 6.33, N 8.82

15

Example 19

A suspension of Starting compound (1.6 g) in dichloromethane (41 ml) was stirred with cooling at 5°C and treated with triethylsilane (1.1 ml), followed by 20 trifluoroacetic acid (5.3 ml) dropwise over 30 minutes. After warming to room temperature, the clear solution was stirred for 2 hours, then poured into 450 ml of pH 6.86 phosphate buffer and adjusted to pH 8.5 with 4N-sodium hydroxide solution. Organic solvent was removed by 25 evaporation and the remaining aqueous solution purified by ODS column chromatography, eluting with aqueous acetonitrile (5-20%). Object compound-containing fractions were pooled, evaporated, and lyophilized to give Object compound (1.25 g) as an amorphous white powder.

30 IR (KBr): 1633.4, 1537.0, 1517.7, 1440.6, 1267.0 cm^{-1}

NMR (DMSO- d_6 , δ): 0.95 (3H, d, $J=6.7\text{Hz}$), 1.12 (3H, d, $J=5.8\text{Hz}$), 1.27 (2H, d, $J=6.6\text{Hz}$), 1.28-1.70 (2H, m), 1.75-2.45 (4H, m), 2.65-3.30 (5H, m), 3.50-4.50 (11H, m), 4.60-4.90 (2H, m), 5.00 (2H, s), 5.05- 35 5.40 (5H, m), 6.70 (2H, d, $J=8.2\text{Hz}$), 6.76 (2H, d,

J=8.2Hz), 6.96 (1H, s), 7.00-7.15 (1H, m), 7.34 (5H, s), 7.40-7.95 (3H, m), 8.60-8.90 (1H, m)

MASS (m/z): 1023.3 (M^+ -H)

Elemental Analysis Calcd. for $C_{43}H_{60}N_8O_{19}S \cdot 6H_2O$:

5 C 45.58, H 6.40, N 9.89

Found: C 45.49, H 6.24, N 9.70

Example 20

10 NMR (DMSO- d_6 , δ): 0.95 (3H, d, J=6.6Hz), 6.67 (1H, d, J=6.9Hz), 6.73-6.75 (1H, m), 6.96 (1H, br s), 7.07 (2H, d, J=8.8Hz), 7.32 (5H, s), 7.73 (2H, d, J=8.7Hz), 7.87 (2H, d, J=8.5Hz), 8.06-8.14 (6H, m), 8.72 (1H, s), 8.80 (1H, d, J=7.1Hz)

15 MASS (m/z): 1465.5 (M^+ -Na)

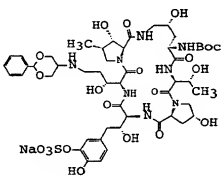
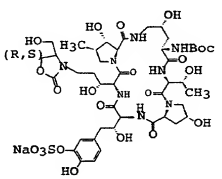
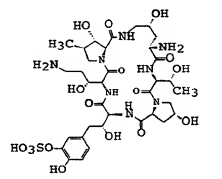
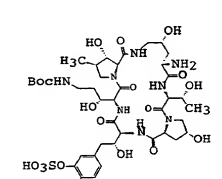
Example 21

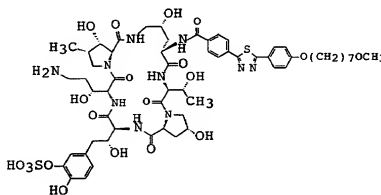
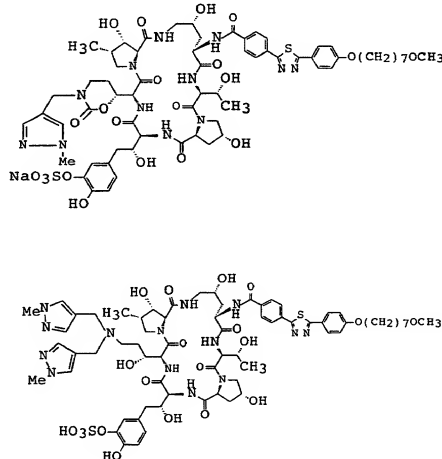
The Object Compound (21) was used directly in the next reaction without purification.

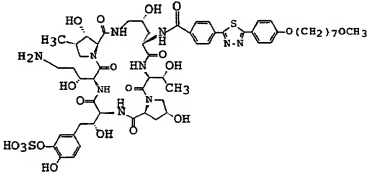
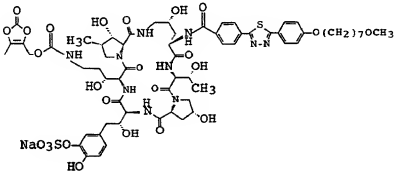
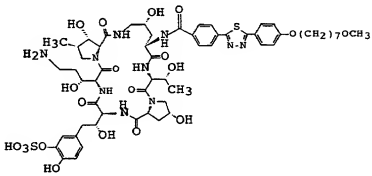
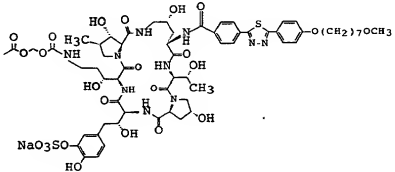
20 The Starting Compounds (22) to (206) used and the Object Compounds (22) to (206) obtained in the following Example 22 to 206 are given in the table as below, in which the formulas of the starting compounds are in the upper column and the formulas of the object compounds are in the lower column,
25 respectively.

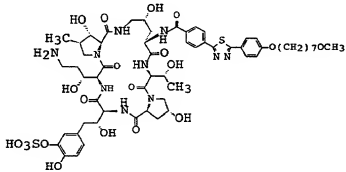
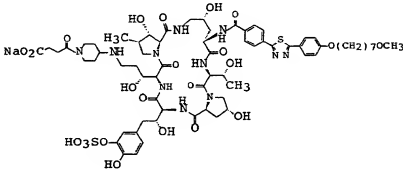
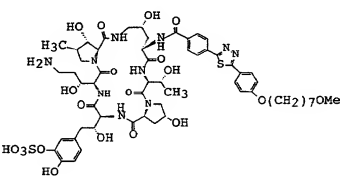
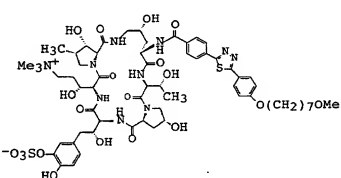
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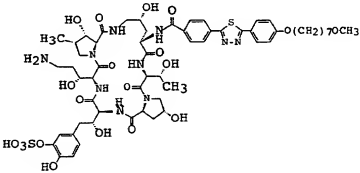
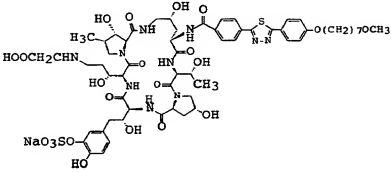
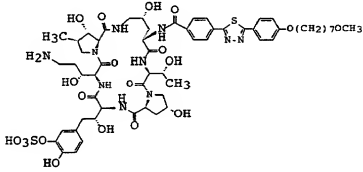
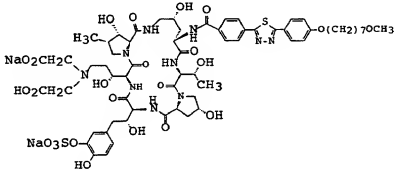
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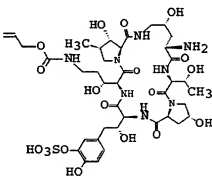
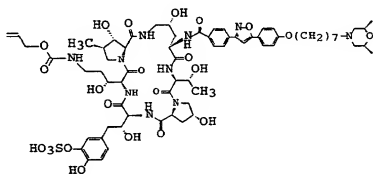
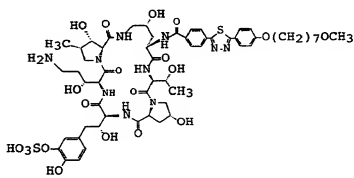
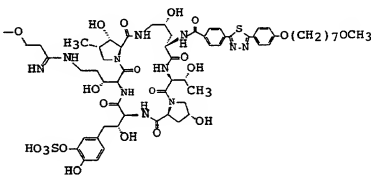
Example No.	Formula
22	
	
23	
	

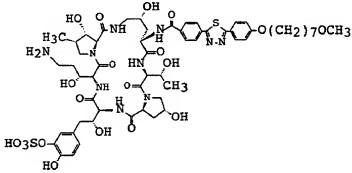
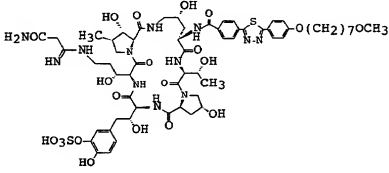
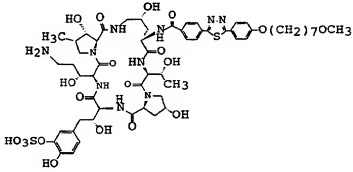
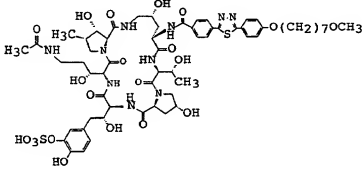
Example No.	Formula
24	
	

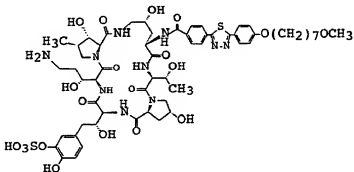
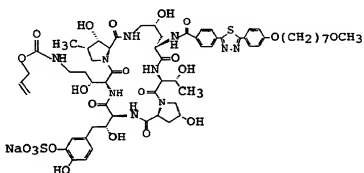
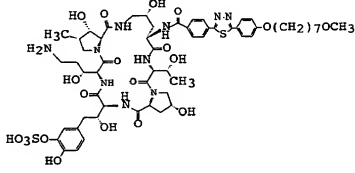
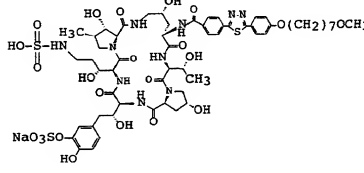
Example No.	Formula
25	
	
26	
	

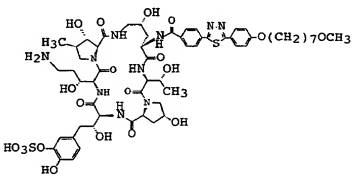
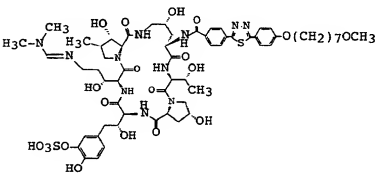
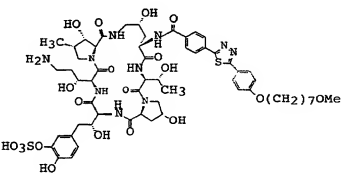
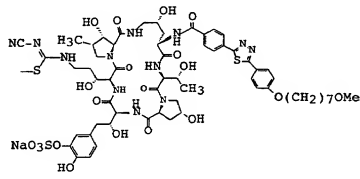
Example No.	Formula
27	
	
28	
	

Example No.	Formula
29	
	
30	
	

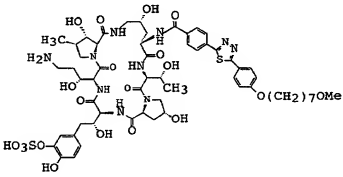
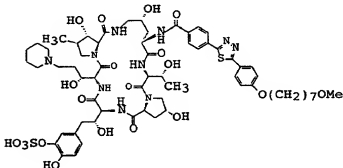
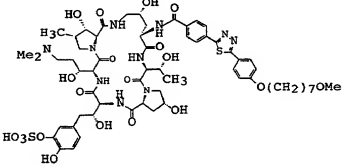
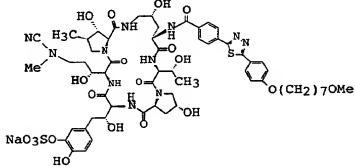
Example No.	Formula
31	
	
32	
	

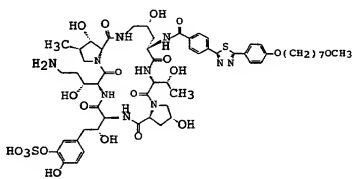
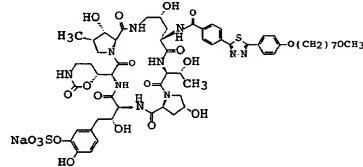
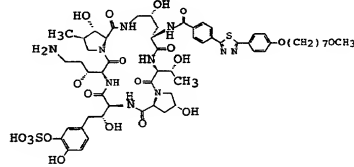
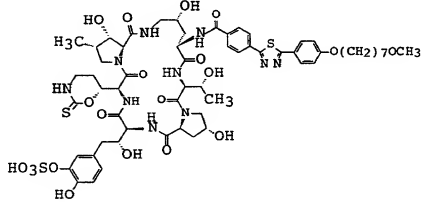
Example No.	Formula
33	
	
34	
	

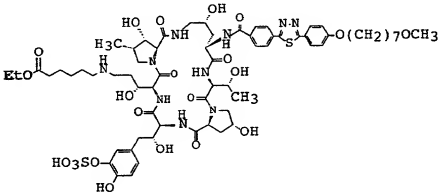
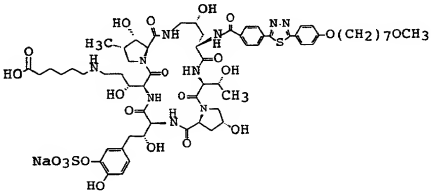
Example No.	Formula
35	
	
36	
	

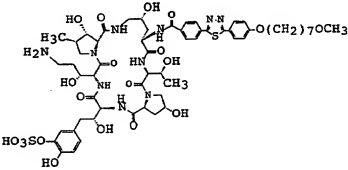
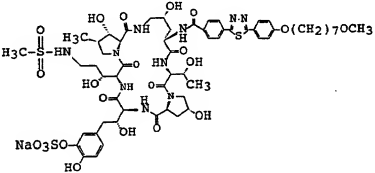
Example No.	Formula
37	
	
38	
	

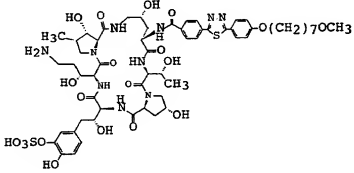
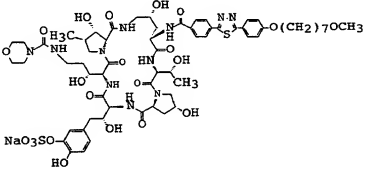
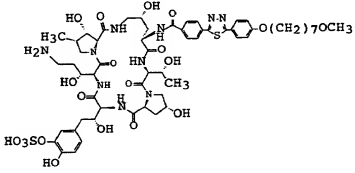
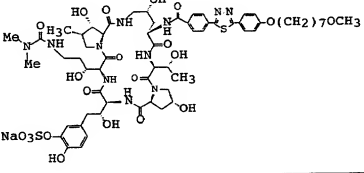
Example No.	Formula
39	
40	

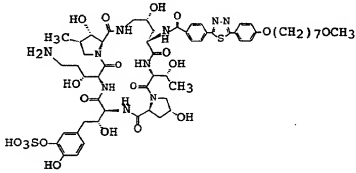
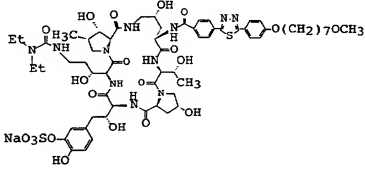
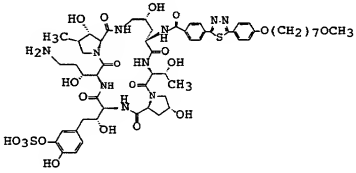
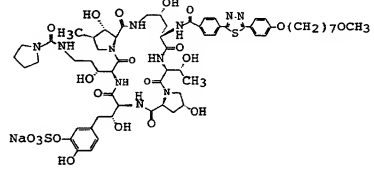
Example No.	Formula
41	
	
42	
	

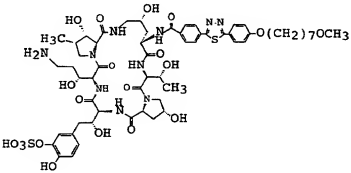
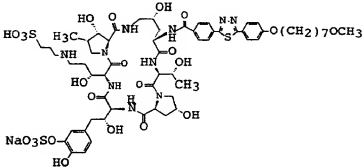
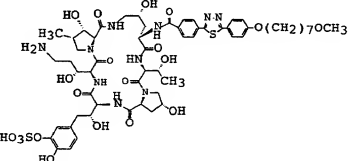
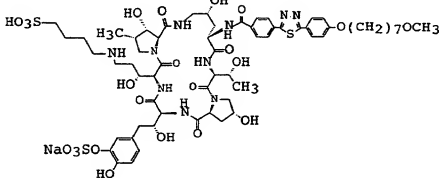
Example No.	Formula
43	 <p>Chemical structure of a complex molecule, likely a derivative of a nucleoside or nucleotide. It features a central sugar moiety (possibly a ribose derivative) linked to a nucleobase (possibly a pyrimidine derivative). The structure includes a sulfonamide group (SO₂NH₂) and a long alkoxy chain (O(CH₂)₇OCH₃). The molecule is shown in a chair conformation.</p>
	 <p>Chemical structure of a complex molecule, similar to the one above, but with a different substitution pattern. It features a central sugar moiety (possibly a ribose derivative) linked to a nucleobase (possibly a pyrimidine derivative). The structure includes a sulfonamide group (SO₂NH₂) and a long alkoxy chain (O(CH₂)₇OCH₃). The molecule is shown in a chair conformation.</p>
44	 <p>Chemical structure of a complex molecule, similar to the ones above, but with a different substitution pattern. It features a central sugar moiety (possibly a ribose derivative) linked to a nucleobase (possibly a pyrimidine derivative). The structure includes a sulfonamide group (SO₂NH₂) and a long alkoxy chain (O(CH₂)₇OCH₃). The molecule is shown in a chair conformation.</p>
	 <p>Chemical structure of a complex molecule, similar to the ones above, but with a different substitution pattern. It features a central sugar moiety (possibly a ribose derivative) linked to a nucleobase (possibly a pyrimidine derivative). The structure includes a sulfonamide group (SO₂NH₂) and a long alkoxy chain (O(CH₂)₇OCH₃). The molecule is shown in a chair conformation.</p>

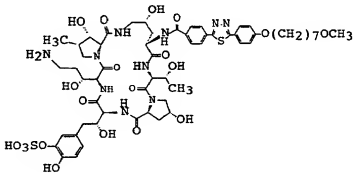
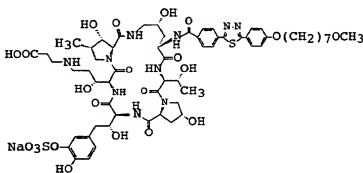
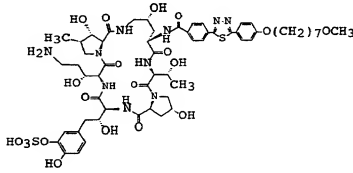
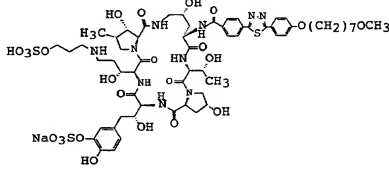
Example No.	Formula
45	 <p>Chemical structure of a complex molecule, likely a derivative of a nucleoside or nucleotide. The structure features a central pyrazole ring system, a thiazolidine ring, and a sulfonamide group. The molecule is labeled with 'EtO' and 'CH3'.</p>
	 <p>Chemical structure of a complex molecule, similar to the one above, but with a different substituent on the sulfonamide group, labeled 'NaO3SO'.</p>

Example No.	Formula
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	deleted
48	
	

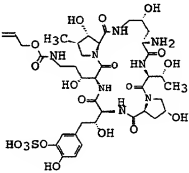
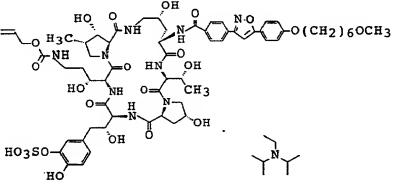
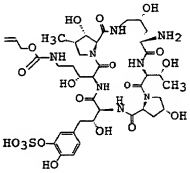
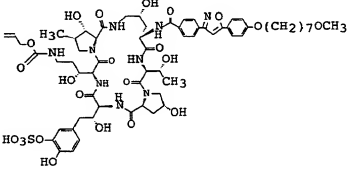
Example No.	Formula
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50	
	

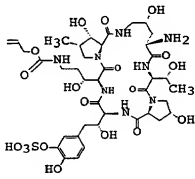
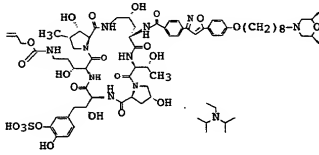
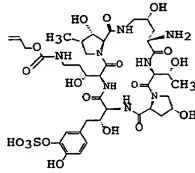
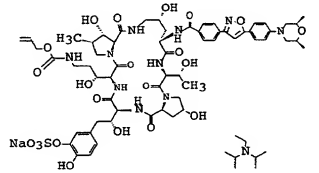
Example No.	Formula
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52	
	

Example No.	Formula
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54	
	

Example No.	Formula
55	
	
56	
	

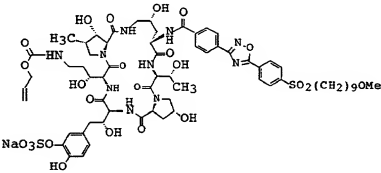
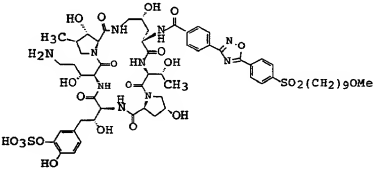
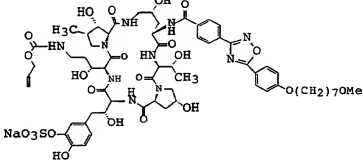
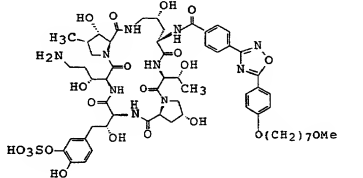
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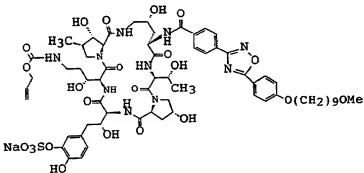
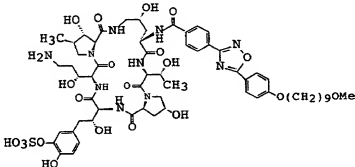
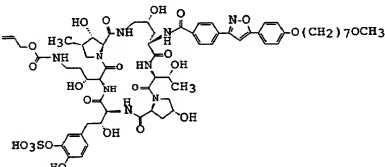
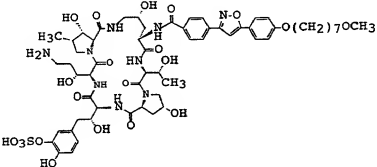
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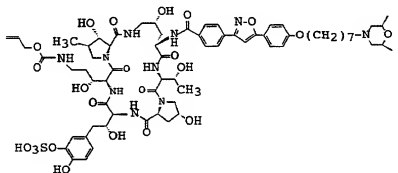
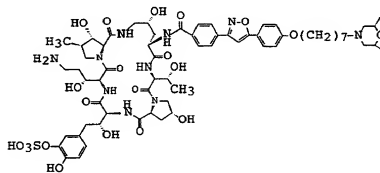
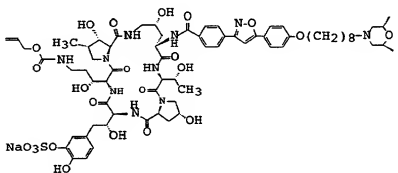
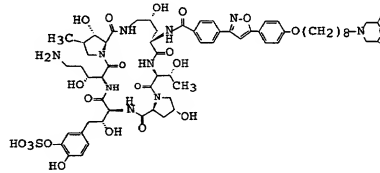
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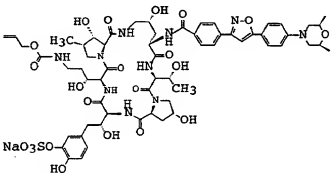
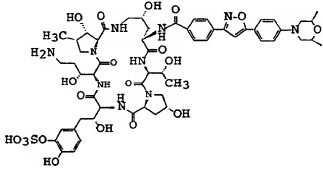
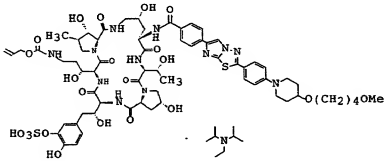
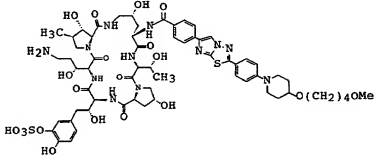
Example No.	Formula
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64	

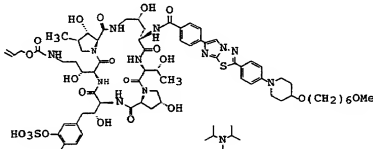
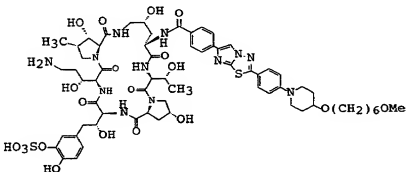
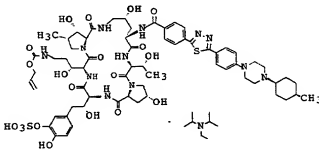
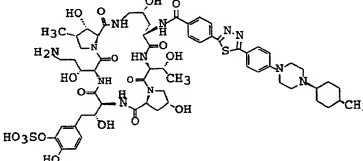
Example No.	Formula
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66	

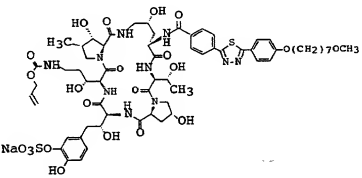
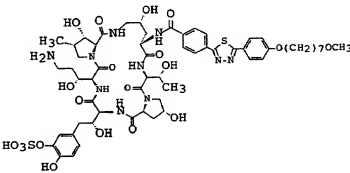
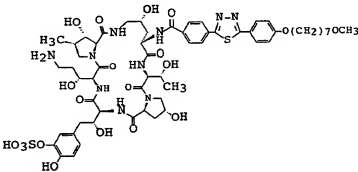
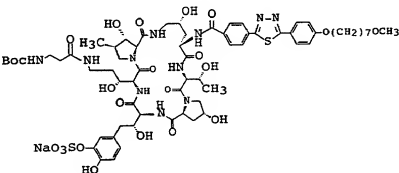
Example No.	Formula
67	
	
68	
	

Example No.	Formula
69	 <p>Chemical structure of Example 69, top part: A complex molecule featuring a central core with multiple hydroxyl groups, a methyl group, and a sodium sulfonate group (NaO₃SO-). It is linked via amide bonds to a side chain containing a 4-(9-methoxyphenoxy)phenyl group.</p>
	 <p>Chemical structure of Example 69, bottom part: Similar to the top part, but with a different side chain configuration, featuring a 4-(9-methoxyphenoxy)phenyl group and a different arrangement of hydroxyl and methyl groups.</p>
70	 <p>Chemical structure of Example 70, top part: A complex molecule featuring a central core with multiple hydroxyl groups, a methyl group, and a sodium sulfonate group (HO₃SO-). It is linked via amide bonds to a side chain containing a 4-(7-methoxyphenoxy)phenyl group.</p>
	 <p>Chemical structure of Example 70, bottom part: Similar to the top part, but with a different side chain configuration, featuring a 4-(7-methoxyphenoxy)phenyl group and a different arrangement of hydroxyl and methyl groups.</p>

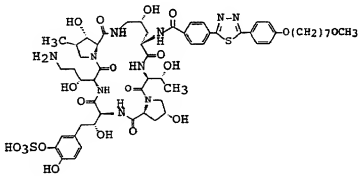
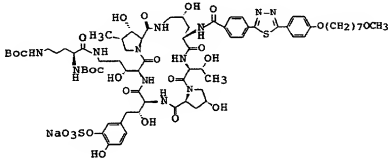
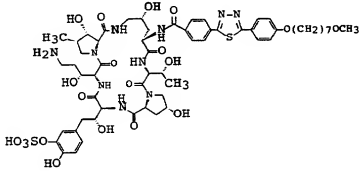
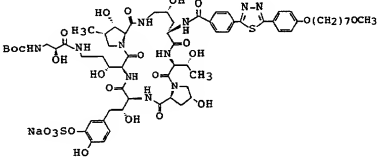
Example No.	Formula
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Example No.	Formula
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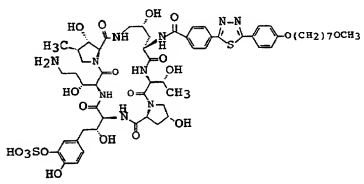
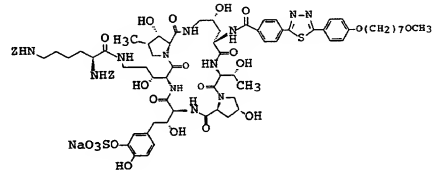
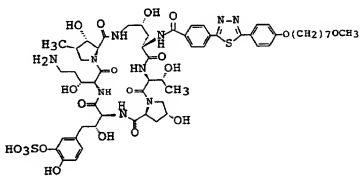
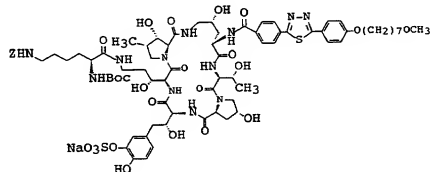
Example No.	Formula
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76	
	

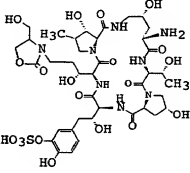
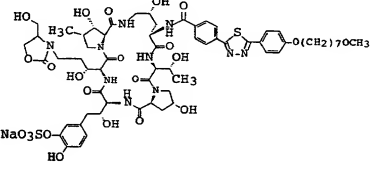
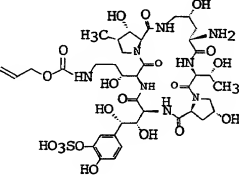
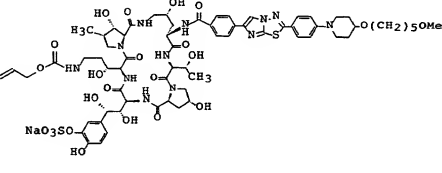
Example No.	Formula
77	 <p>Chemical structure of a complex molecule, likely a derivative of a nucleoside or nucleotide. It features a central core with multiple hydroxyl groups, a sodium sulfonate group (NaO₃SO), and a long alkoxy chain (O(CH₂)₇OCH₃).</p>
	 <p>Chemical structure of a complex molecule, likely a derivative of a nucleoside or nucleotide. It features a central core with multiple hydroxyl groups, a sulfonate group (HO₃SO), and a long alkoxy chain (O(CH₂)₇OCH₃).</p>
78	 <p>Chemical structure of a complex molecule, likely a derivative of a nucleoside or nucleotide. It features a central core with multiple hydroxyl groups, a sulfonate group (HO₃SO), and a long alkoxy chain (O(CH₂)₇OCH₃).</p>
	 <p>Chemical structure of a complex molecule, likely a derivative of a nucleoside or nucleotide. It features a central core with multiple hydroxyl groups, a sodium sulfonate group (NaO₃SO), and a long alkoxy chain (O(CH₂)₇OCH₃).</p>

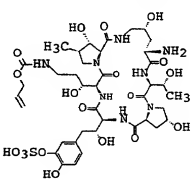
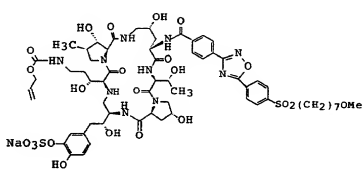
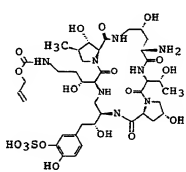
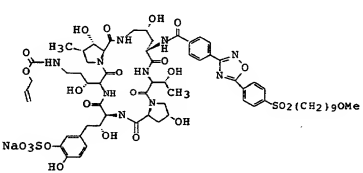
Example No.	Formula
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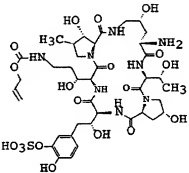
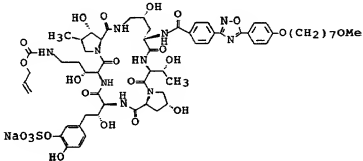
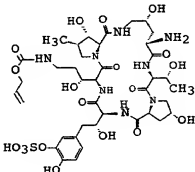
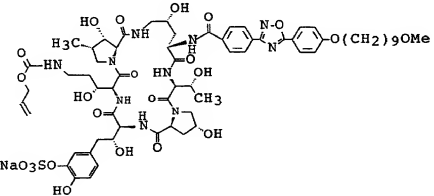
Example No.	Formula
81	 <p>Chemical structure of a complex molecule. It features a central core with multiple hydroxyl groups, a sulfonate group (HO₃SO-), and a long alkoxy chain (O(CH₂)₇OCH₃). The structure is highly branched and includes several amide and ester linkages.</p>
	 <p>Chemical structure of a complex molecule, similar to the one above, but with a Boc group (BocHN-) and a different sulfonate group (NaO₃SO-).</p>
82	 <p>Chemical structure of a complex molecule, similar to the one above, but with a different sulfonate group (HO₃SO-).</p>
	 <p>Chemical structure of a complex molecule, similar to the one above, but with a Boc group (BocHN-) and a different sulfonate group (NaO₃SO-).</p>

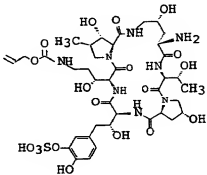
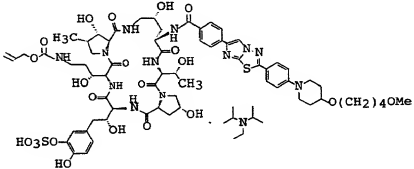
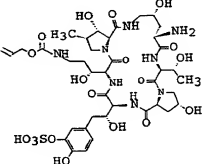
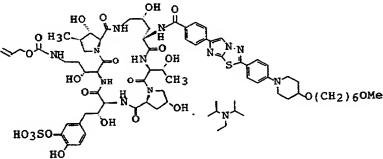
Example No.	Formula
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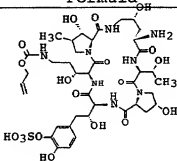
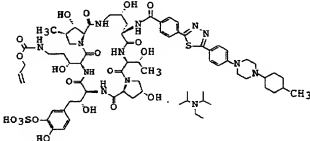
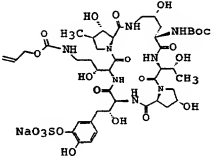
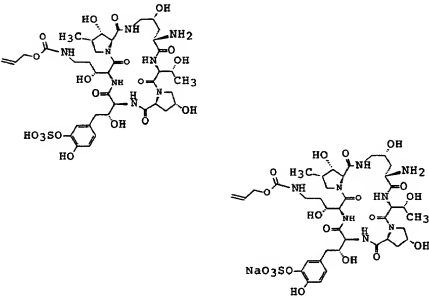
Example No.	Formula
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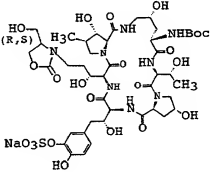
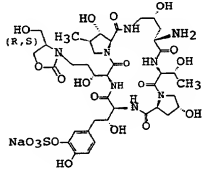
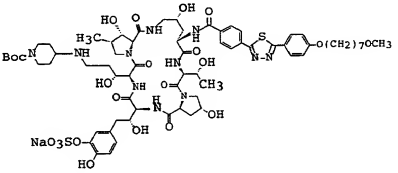
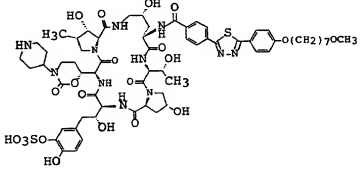
Example No.	Formula
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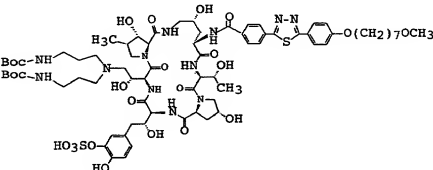
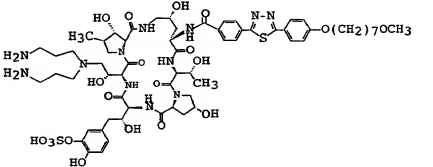
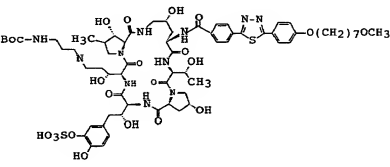
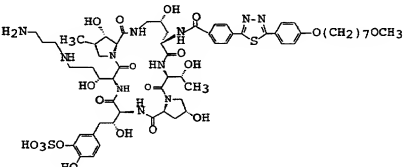
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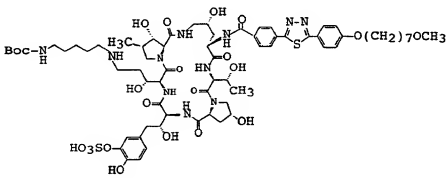
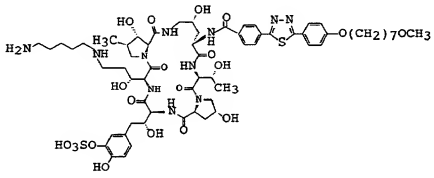
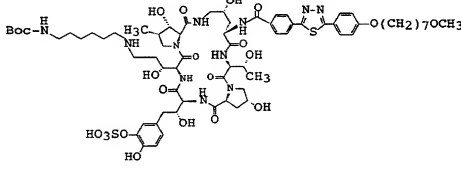
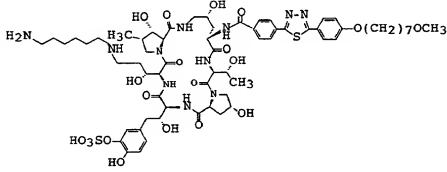
Example No.	Formula
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Example No.	Formula
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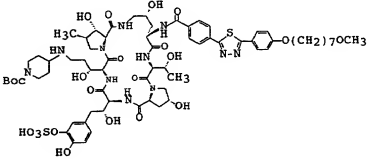
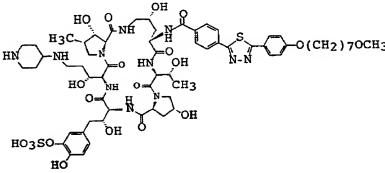
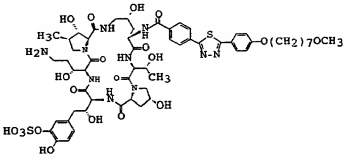
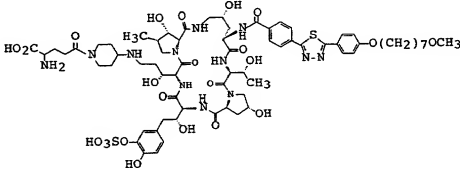
Example No.	Formula
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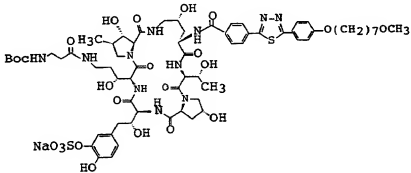
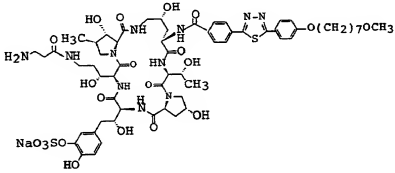
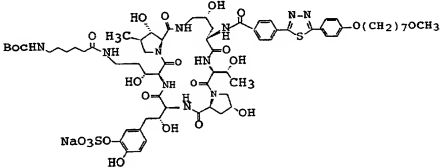
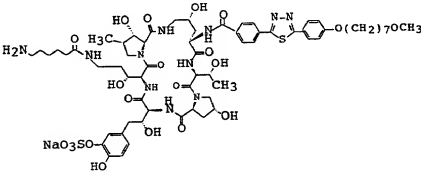
Example No.	Formula
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100	
	

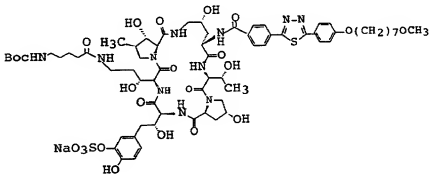
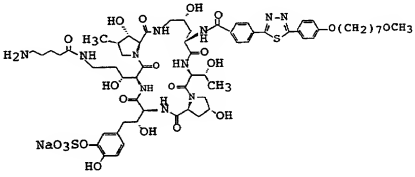
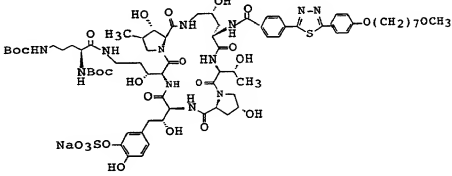
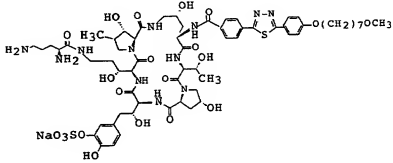
Example No.	Formula
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102	
	

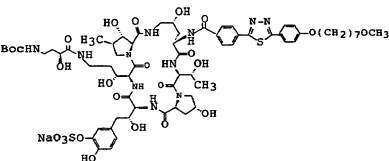
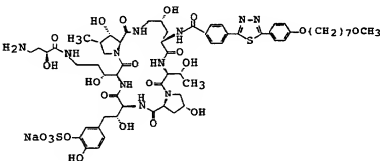
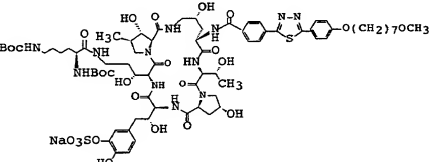
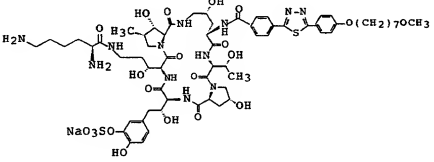
Example No.	Formula
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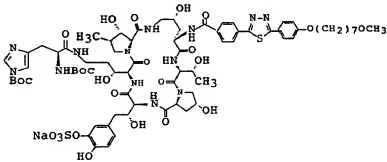
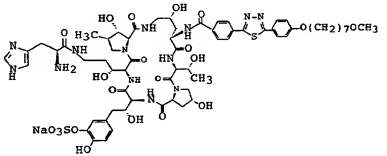
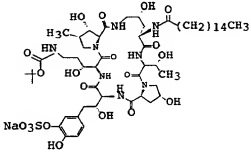
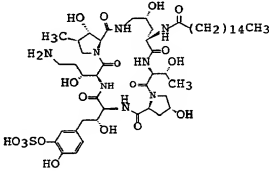
Example No.	Formula
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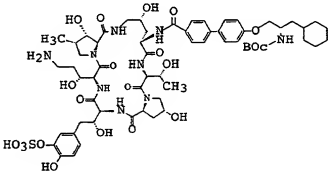
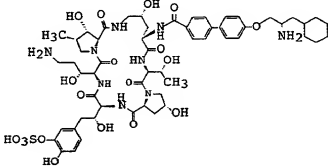
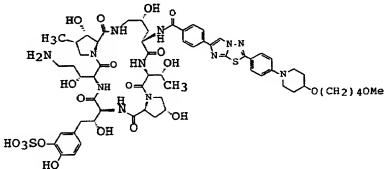
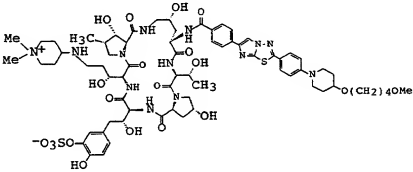
Example No.	Formula
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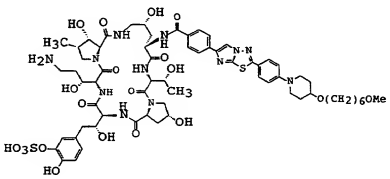
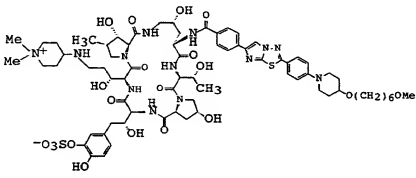
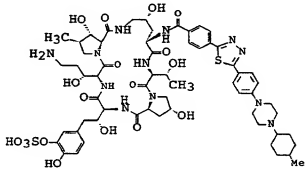
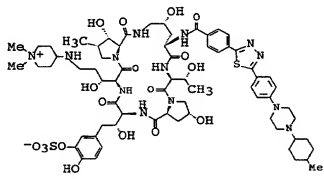
Example No.	Formula
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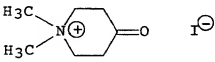
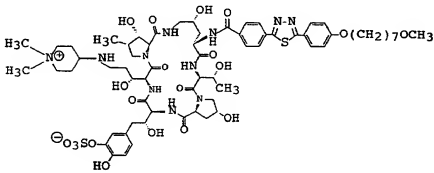
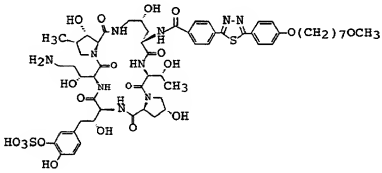
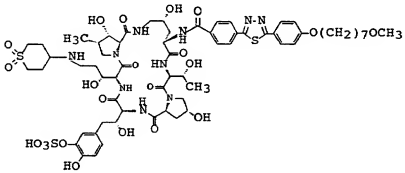
Example No.	Formula
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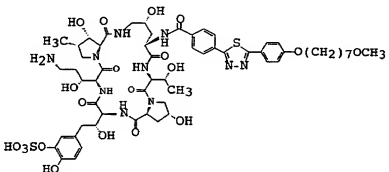
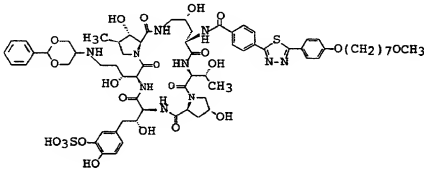
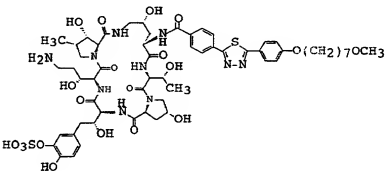
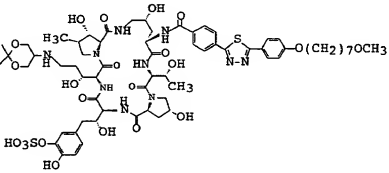
Example No.	Formula
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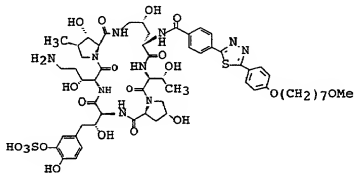
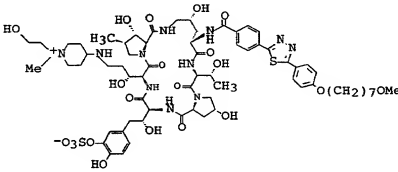
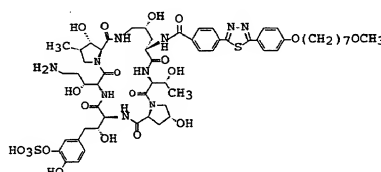
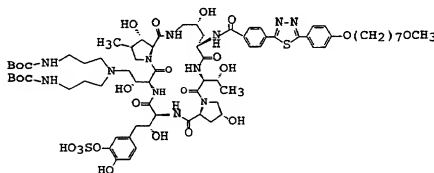
Example No.	Formula
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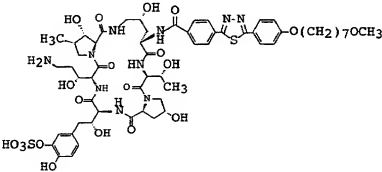
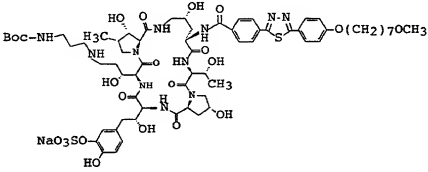
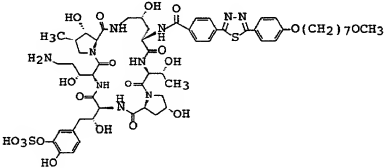
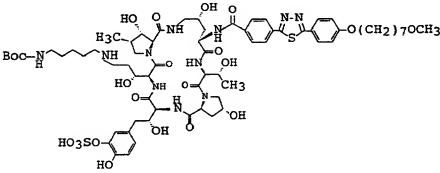
Example No.	Formula
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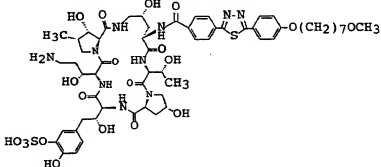
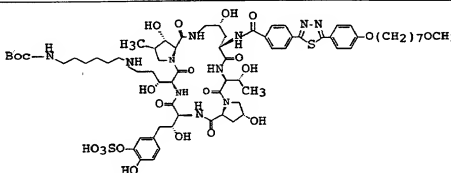
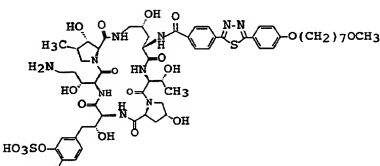
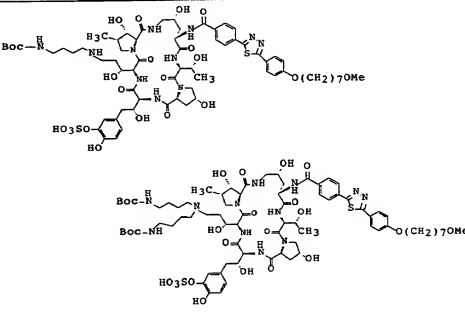
Example No.	Formula
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Example No.	Formula
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122	
	

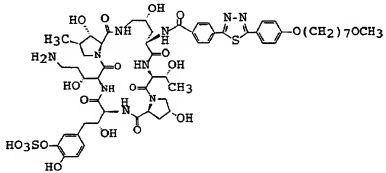
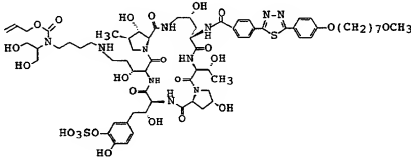
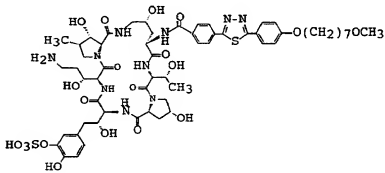
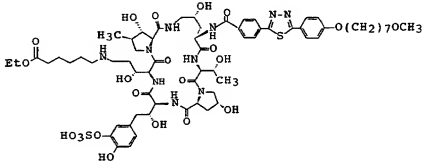
Example No.	Formula
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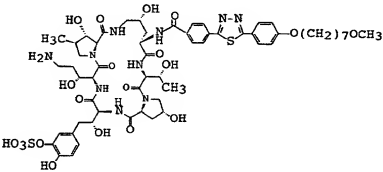
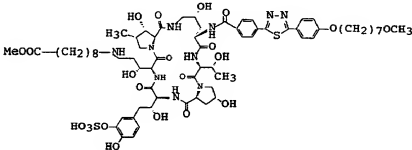
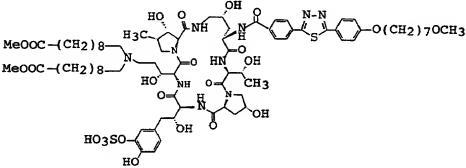
Example No.	Formula
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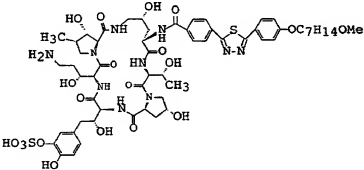
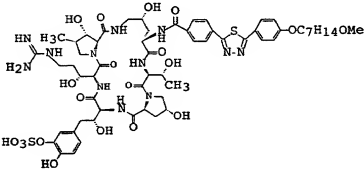
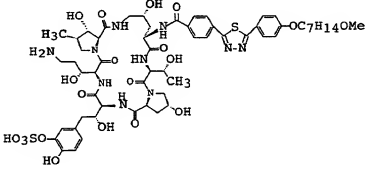
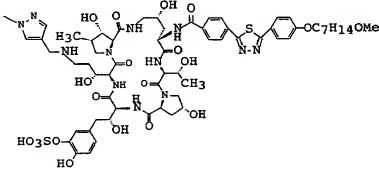
Example No.	Formula
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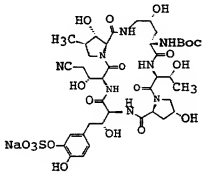
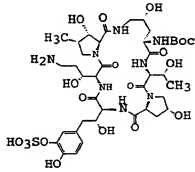
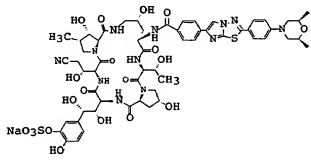
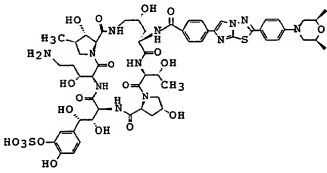
Example No.	Formula
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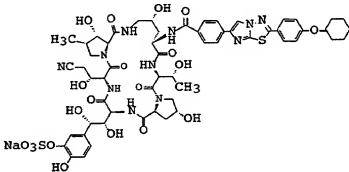
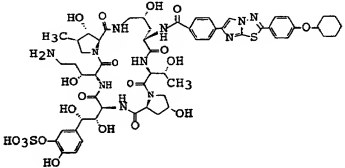
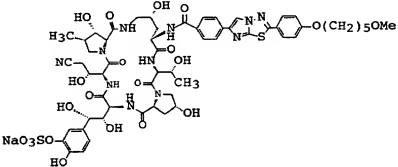
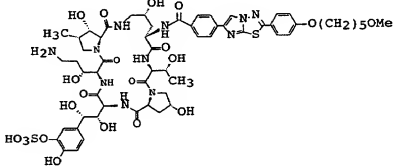
Example No.	Formula
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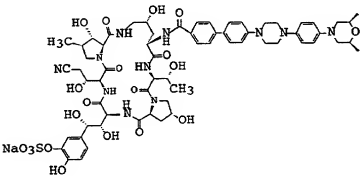
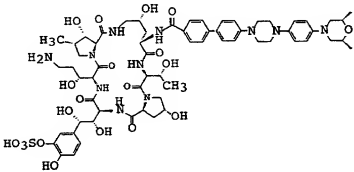
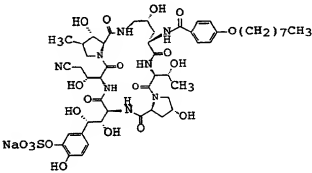
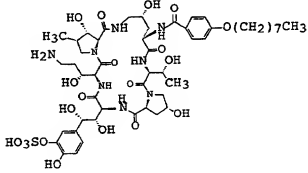
Example No.	Formula
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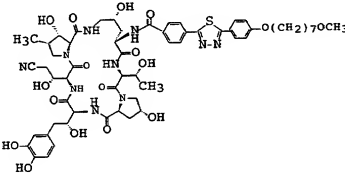
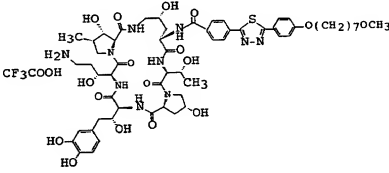
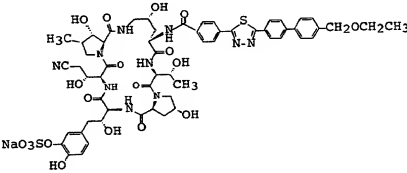
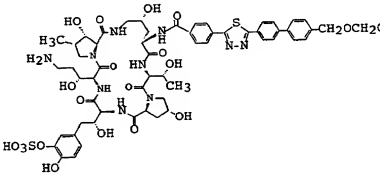
Example No.	Formula
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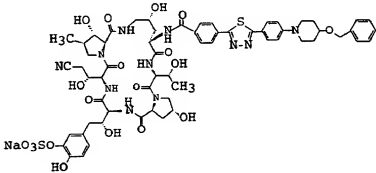
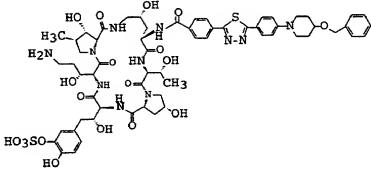
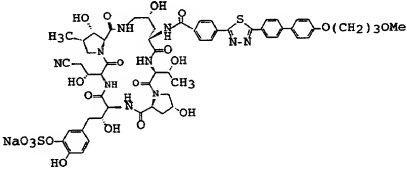
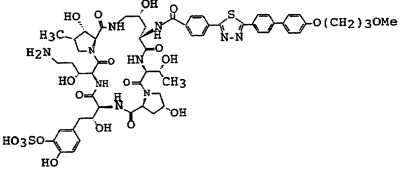
Example No.	Formula
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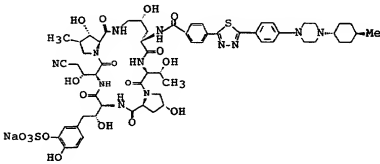
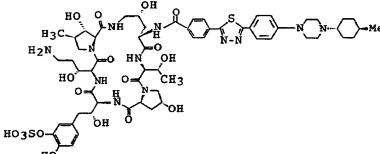
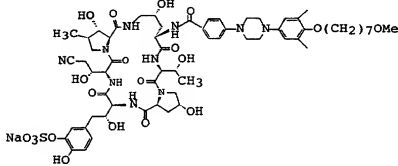
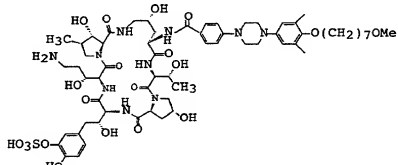
Example No.	Formula
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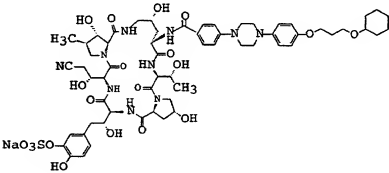
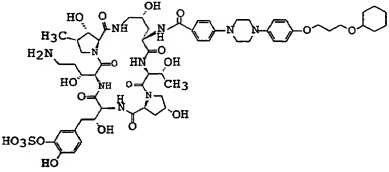
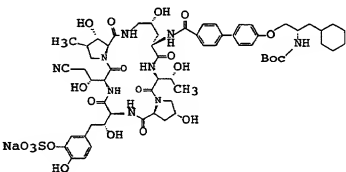
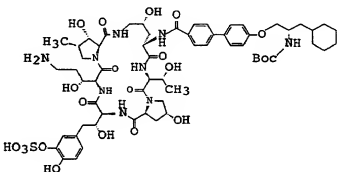
Example No.	Formula
140	
	
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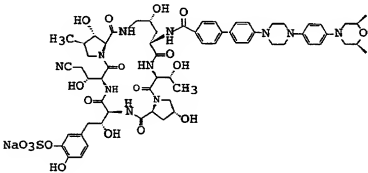
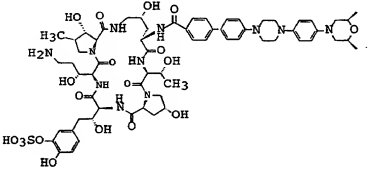
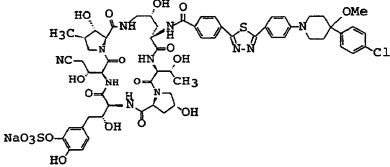
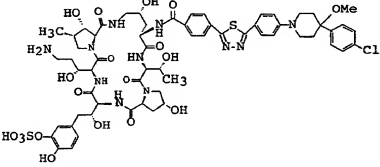
Example No.	Formula
142	
	
143	
	

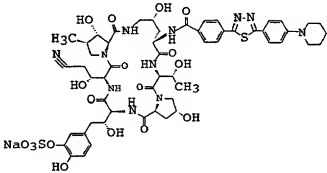
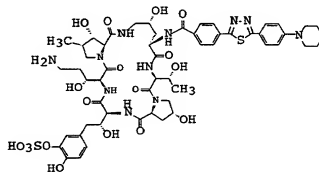
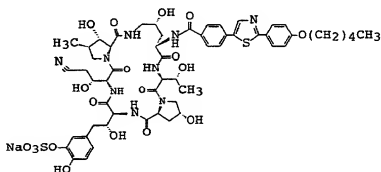
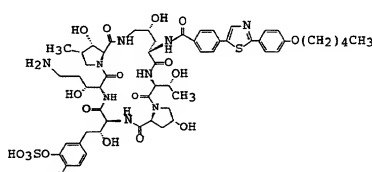
Example No.	Formula
144	
	
145	
	

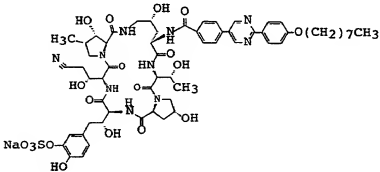
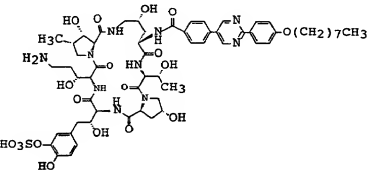
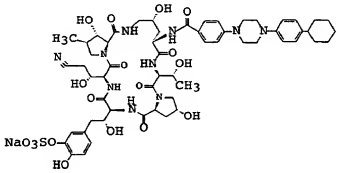
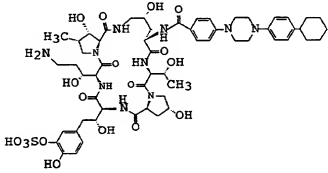
Example No.	Formula
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147	
	

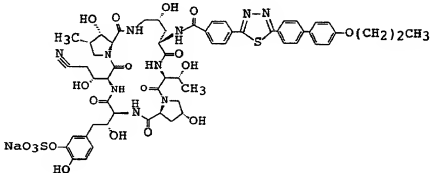
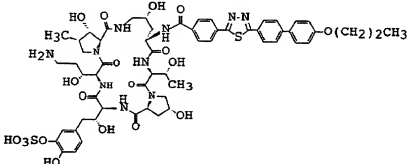
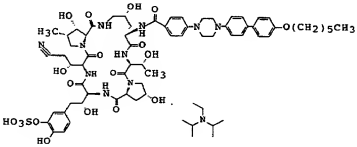
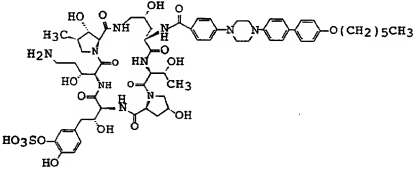
Example No.	Formula
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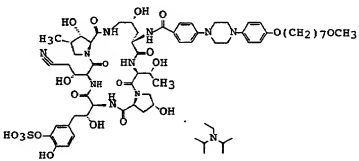
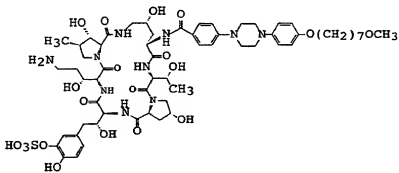
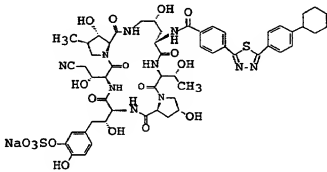
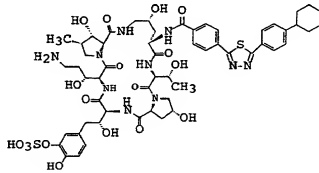
Example No.	Formula
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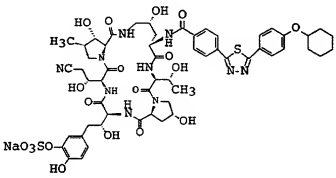
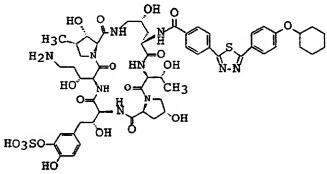
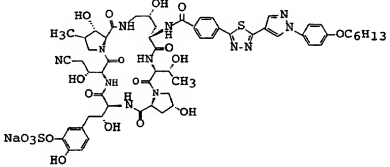
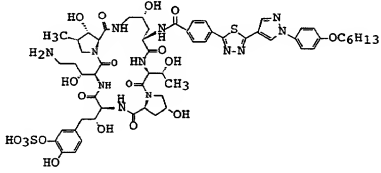
Example No.	Formula
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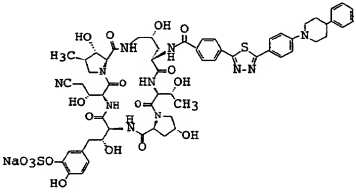
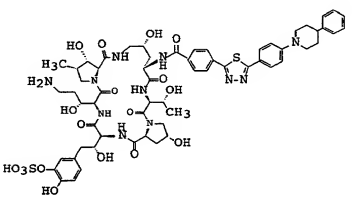
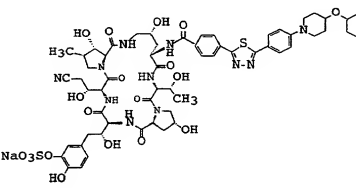
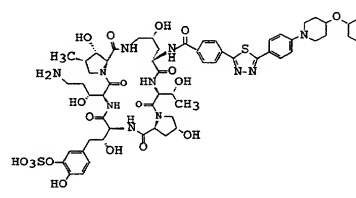
Example No.	Formula
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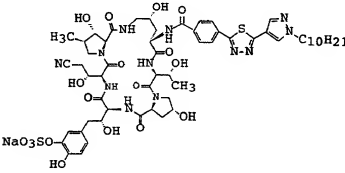
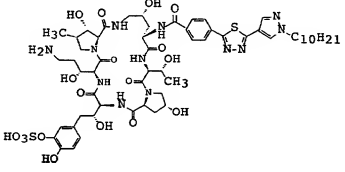
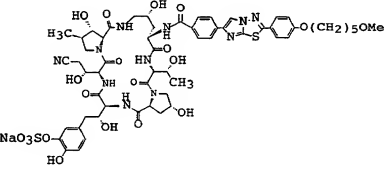
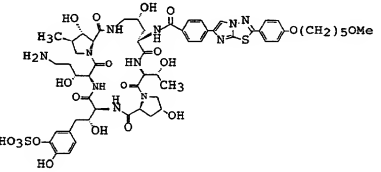
Example No.	Formula
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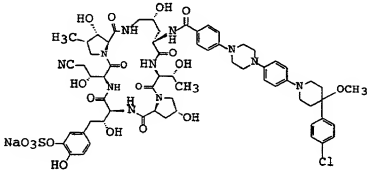
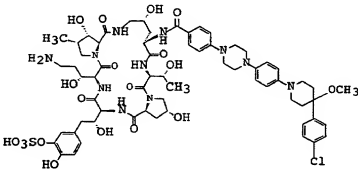
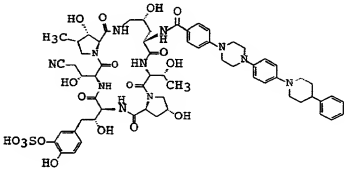
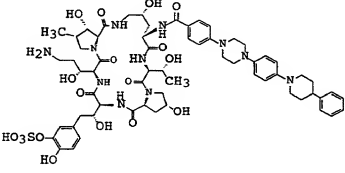
Example No.	Formula
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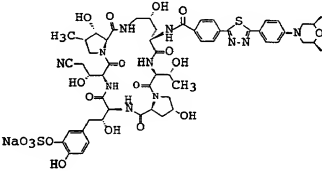
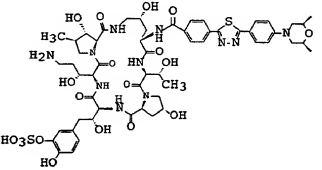
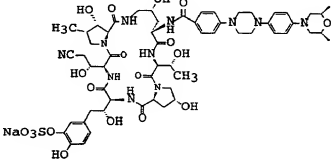
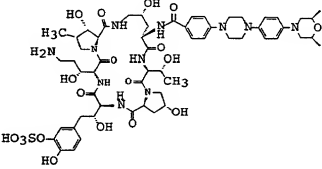
Example No.	Formula
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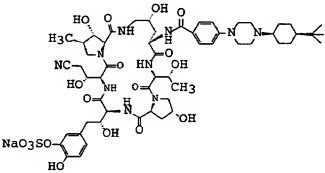
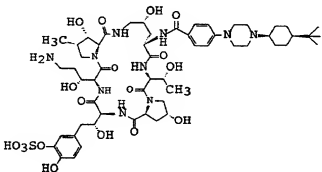
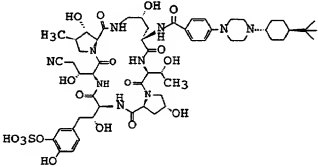
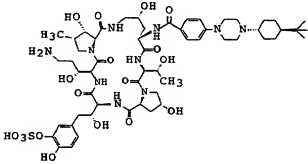
Example No.	Formula
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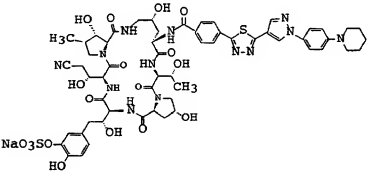
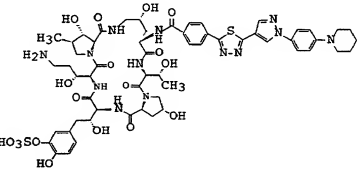
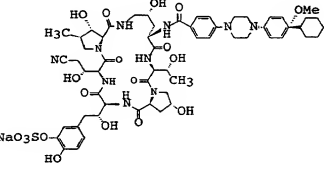
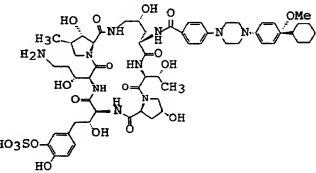
Example No.	Formula
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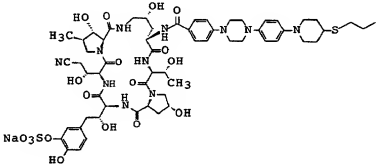
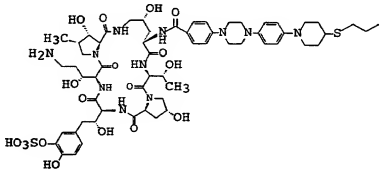
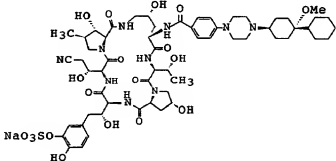
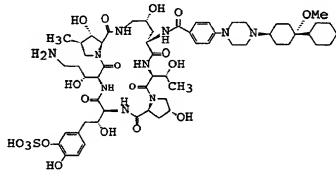
Example No.	Formula
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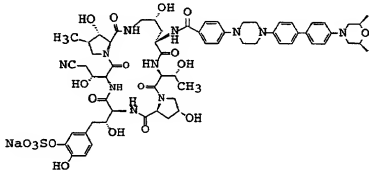
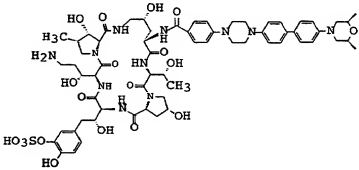
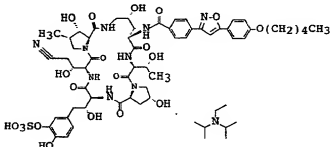
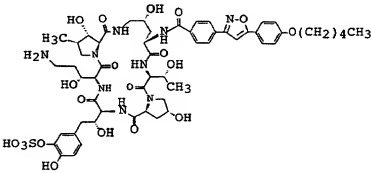
Example No.	Formula
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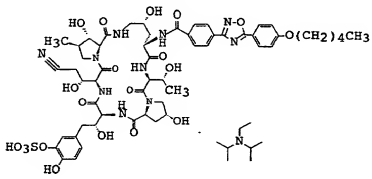
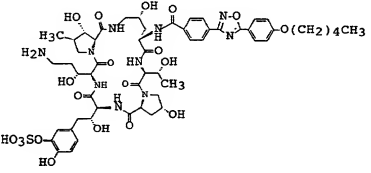
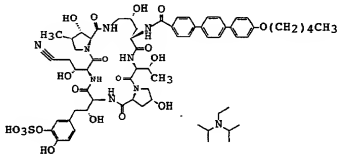
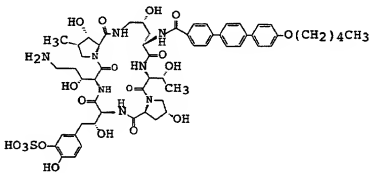
Example No.	Formula
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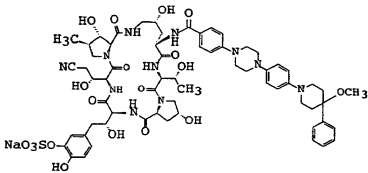
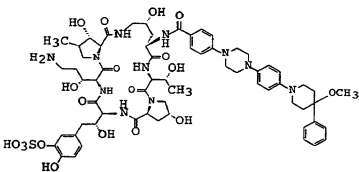
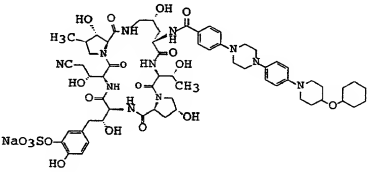
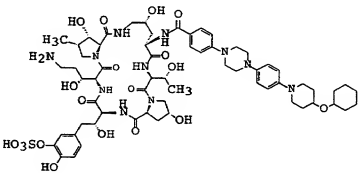
Example No.	Formula
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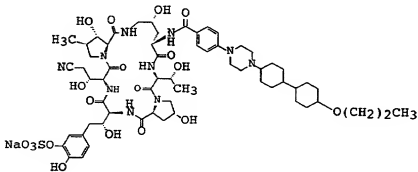
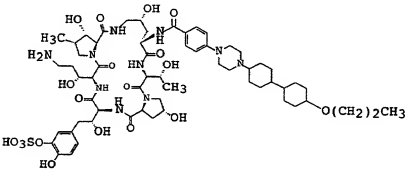
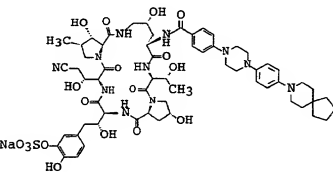
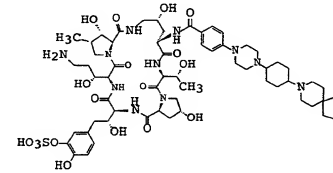
Example No.	Formula
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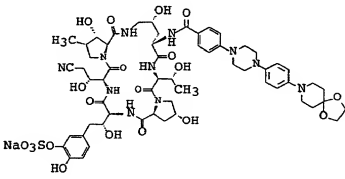
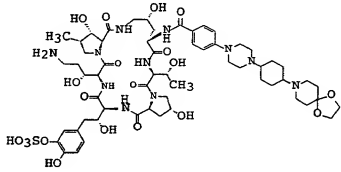
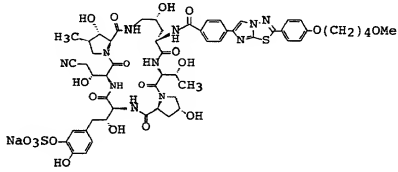
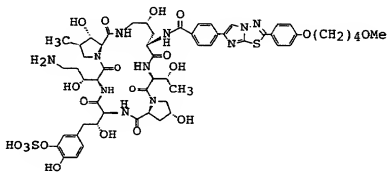
Example No.	Formula
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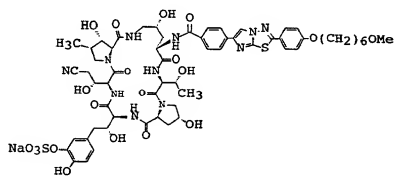
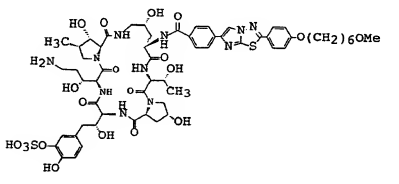
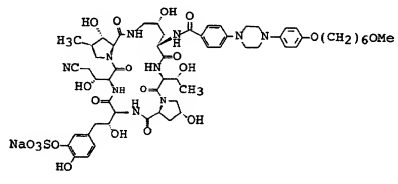
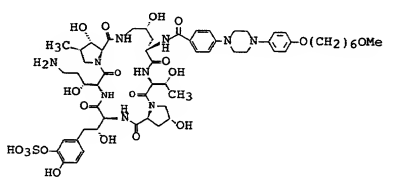
Example No.	Formula
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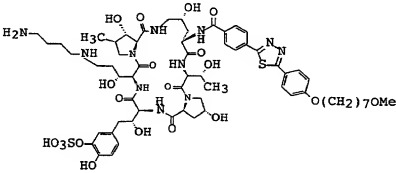
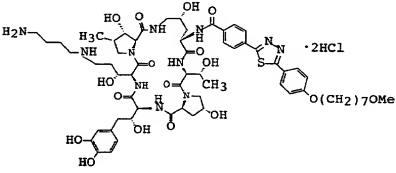
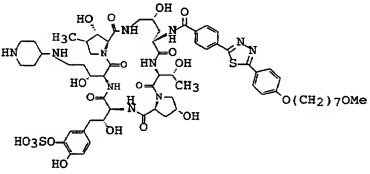
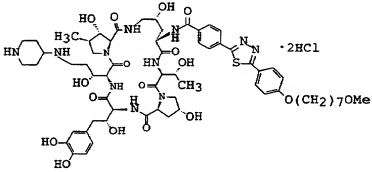
Example No.	Formula
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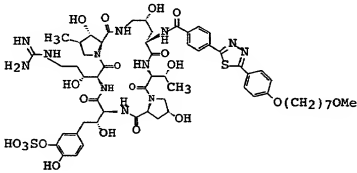
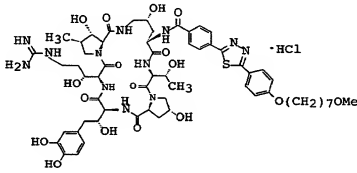
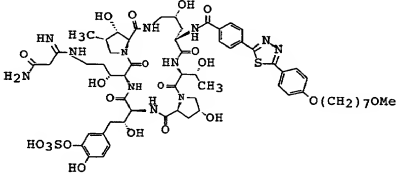
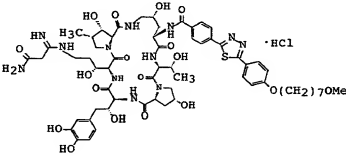
Example No.	Formula
184	
	
185	
	

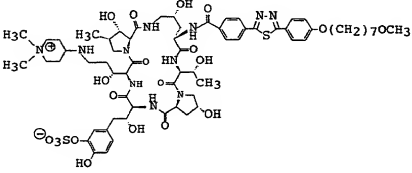
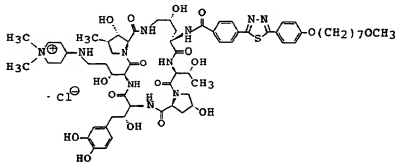
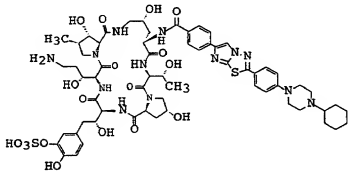
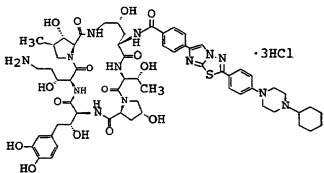
Example No.	Formula
186	
	
187	
	

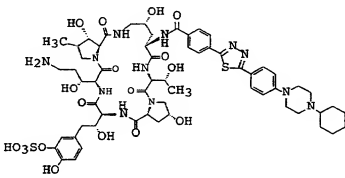
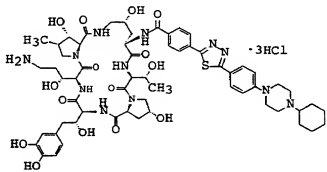
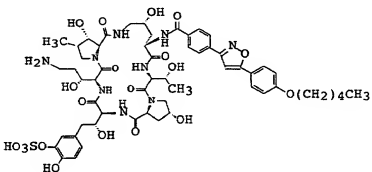
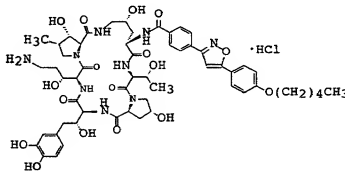
Example No.	Formula
188	
	
189	
	

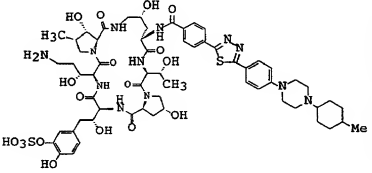
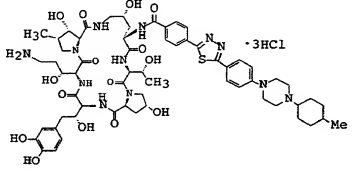
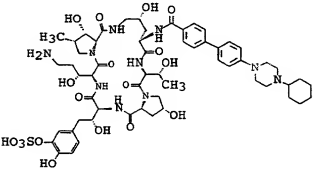
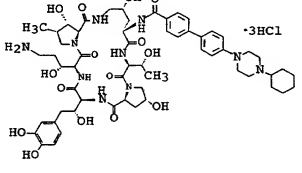
Example No.	Formula
190	
	
191	
	

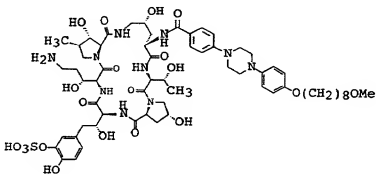
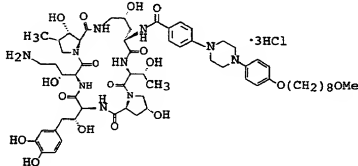
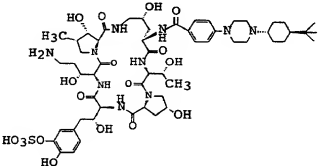
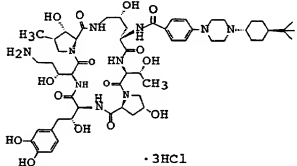
Example No.	Formula
194	
	
195	
	

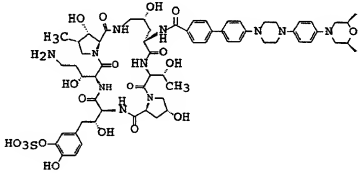
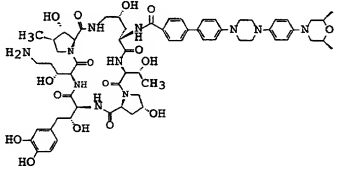
Example No.	Formula
196	
	
197	
	

Example No.	Formula
198	
	
199	
	

Example No.	Formula
200	
	
201	
	

Example No.	Formula
202	
	
203	
	

Example No.	Formula
204	
	
205	
	

Example No.	Formula
206	
	

Example 22

A solution of starting compound (22) (670 mg) and 10% palladium on carbon (50%, including water) (0.8 g) in a mixture of methanol (10 ml) and water (10 ml) was hydrogenated under an atmospheric pressure of hydrogen with stirring at ambient temperature for 12 hours. The catalyst was filtered off and washed with a mixture of methanol and water (1:1 v/v) (50 ml), and the filtrate and washes were combined. To the solution was added dropwise allyloxycarbonyl chloride (3.0 ml) adjusting pH to 8.5-10.0 with 1N sodium hydroxide with stirring on an ice-bath. The mixture was stirred at the same temperature for 2 hours and concentrated in vacuo. The resulting residue was dissolved in 1N sodium hydroxide (20 ml) and allowed to stand at 4°C overnight. The solution was subjected to column

chromatography on ODS (Daiso-gel, SP-120-40/60-ODS-B (Trademark: prepared by Daiso Co., Ltd.)) (100 ml) eluting with 10% acetonitrile in water. The fractions containing the object compound were collected and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give object compound (22) (379 mg).

NMR (DMSO- d_6 + D₂O, δ): 0.96 (3H, d, J=6.73Hz), 1.07 (3H, broad s), 1.36 (9H, s), 1.40-2.40 (8H, m), 2.70-3.45 (5H, m), 2.01 (3H, d, J=4.26Hz), 3.21 (3H, s), 3.31 (4H, t, J=6.34Hz), 3.70-4.50 (14H, m), 4.85-4.90 (2H, m), 3.60-4.95 (18H, m), 6.69 (1H, d, J=8.25Hz), 6.75 (1H, d, J=9.54Hz), 6.98 (1H, s)

ESI MASS (m/z) (Negative): 1135.3 (M^+ +Na)

Example 23

To a solution of starting compound (23) (1.0 g) in DMF (10 ml) were added 2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile (0.30 g) and diisopropylethylamine (0.27 ml) with stirring at ambient temperature, and the mixture was stirred at the same temperature for 2 hours. To the reaction mixture was added pH 6.86 standard buffer solution (100 ml), and the solution was subjected to column chromatography on ODS (Daiso-gel, SP-120-40/60-ODS-B (Trademark: prepared by Daiso Co., Ltd.)) (100 ml) eluting with 20% acetonitrile in water. The fractions containing the object compound were collected and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give object compound (23) (302 mg).

IR (KBr): 1668, 1633, 1516, 1441, 1277, 1252 cm^{-1}

NMR (DMSO- d_6 + D₂O, δ): 0.97 (3H, d, J=6.64Hz), 1.07 (3H, d, J=5.96Hz), 1.37 (9H, s), 1.40-2.00 (4H, m), 2.10-2.50 (4H, m), 2.60-3.40 (6H, m), 3.60-4.50 (10H, m), 4.65-4.85 (2H, m), 6.71 (1H, d, J=8.14Hz), 6.78 (1H, d, J=8.39Hz), 6.98 (1H, s)

ESI MASS (m/z) (Negative): 989.3 ($M^{+}-1$)

Elemental Analysis Calcd. for $C_{40}H_{62}N_8O_{19}S \cdot 5H_2O$:

C 44.44, H 6.71, N 10.36

Found: C 44.23, H 6.42, N 9.82

5

Example 24

A solution of starting compound (24) (211 mg), 1-methylpyrazole-4-carboxaldehyde (21.4 mg), acetic acid (29.2 mg) and sodium cyanoborohydride (13.3 mg) in 1:1 methanol-N,N-dimethylformamide (6 ml) was stirred 2 days at room temperature, then treated with ethyl acetate and the precipitate was collected, washed with ethyl acetate and dried. This crude material was dissolved in N,N-dimethylformamide (3 ml), then treated with diisopropylethylamine (42 mg) and 1,1'-carbonyldiimidazole (34.2 mg). After 2 hours at room temperature, further diisopropylethylamine (42 mg) and 1,1'-carbonyldiimidazole (34.2 mg) were added. After 4 hours, the solution was diluted with pH 6.86 standard buffer solution and the solution was subjected to ODS column chromatography eluting with acetonitrile in water mixtures. Fractions containing the object compounds were pooled, evaporated and lyophilized separately to afford major object compound (24) (60 mg) and minor object compound (24) (55 mg) as white amorphous powders.

major object compound (24)

IR (KBr): 2935, 1658.5, 1635, 1444, 1259 cm^{-1}

NMR (DMSO- d_6 + D_2O , δ): 0.9-1.05 (6H, m), 1.23-5.00

(43H, m), 3.22 (3H, s), 3.33 (2H, t, $J=6.6Hz$), 3.69 (3H, s), 6.76 (1H, d, $J=7.7Hz$), 6.81-6.86 (1H, m), 7.07 (1H, br s), 7.15 (2H, d, $J=9Hz$), 7.43 (1H, s), 7.68 (1H, s), 7.94-8.19 (6H, m)

MASS (m/z): 1417.4 ($M^{+}-Na$)

Elemental Analysis Calcd. for $C_{64}H_{81}N_{12}O_{21}S_2Na \cdot 5H_2O$:

C 50.19, H 5.99, N 10.97

35

Found: C 50.16, H 6.06, N 10.82

minor object compound (24)

IR (KBr): 2935, 2862, 1658.5, 1635, 1529, 1516, 1444,
1412, 1257 cm^{-1}

NMR ($\text{DMSO-d}_6 + \text{D}_2\text{O}$, δ): 0.98 (3H, d, $J=6.3\text{Hz}$), 1.05 (3H,
d, $J=5.4\text{Hz}$), 1.2-4.9 (54H, complex m), 3.21 (3H,
s), 3.31 (2H, t, $J=6.4\text{Hz}$), 6.7-6.75 (2H, m), 7.05
(1H, br s), 7.14 (2H, d, $J=8.8\text{Hz}$), 7.4-8.14 (8H,
complex m)

MASS (m/z): 1486.5 (M^+)

Elemental Analysis Calcd. for $\text{C}_{68}\text{H}_{90}\text{N}_{14}\text{O}_{20}\text{S}_2\cdot 6\text{H}_2\text{O}$:

C 51.18, H 6.44, N 12.29

Found: C 51.00, H 6.31, N 11.81

Example 25

To a solution of starting compound (25) (1.5 g) and
(1,3-dioxy-2-oxo-4-cyclopenten-5-yl)-
methoxycarbonyloxysuccinimide (0.47 g) in dimethylformamide
(15 ml) was added diisopropylethylamine (0.302 ml) and
stirred for 5 hours at ambient temperature. The reaction
mixture was pulverized with ethyl acetate. The precipitate
was collected by filtration and dried under reduced pressure.

The powder was added to pH 6.86 buffer and subjected to
column chromatography on ODS (YMC-gel ODS-AM-S-50)
(Trademark: prepared by Yamamura Chemical Lab.) and eluted
with 5-15% acetonitrile aq. The fractions containing the
object compound were combined and evaporated under reduced
pressure to remove acetonitrile. The residue was lyophilized
to give object compound (25) (1.05 g).

IR (KBr): 3350, 1816.6; 1635.3, 1257.4 cm^{-1}

NMR (DMSO-d_6 , δ): 0.96 (3H, d, $J=6.6\text{Hz}$), 1.12 (3H, d,
 $J=5.8\text{Hz}$), 1.2-2.6 (17H, m), 2.13 (3H, s), 2.8-3.4
(7H, m), 3.21 (3H, s), 3.6-5.3 (28H, m), 6.72 (1H,
d, $J=8.2\text{Hz}$), 6.78 (1H, d, $J=8.2\text{Hz}$), 6.88 (1H, s),

7.13 (2H, d, J=8.6Hz), 7.25-7.8 (4H, m), 7.93 (2H, d, J=8.6Hz), 8.09 (4H, s), 8.73 (1H, s), 8.80 (1H, d, J=6.7Hz)

ESI MASS (m/z): 1453 (M^+ -Na)

5 Elemental Analysis Calcd. for $C_{64}H_{81}N_{10}O_{25}S_2Na \cdot 5H_2O$:

C 49.04, H 5.85, N 8.94

Found: C 48.98, H 5.75, N 9.05

Example 26

10 To a solution of starting compound (26) (0.2 g) and 4-acetyloxymethoxycarbonyloxynitrobenzene (58.9 mg) in dimethylformamide (1.5 ml) was added diisopropylethylamine (0.04 ml) and stirred for 5 hours at ambient temperature. The reaction mixture was pulverized with ethyl acetate. The
15 precipitate was collected by filtration and dried under reduced pressure. The powder was added to pH 6.86 buffer and subjected to column chromatography on ODS (YMC-gel ODS-AM-S-50) (Trademark: prepared by Yamamura Chemical Lab.) and eluted with 5-15% acetonitrile aq. The fractions containing
20 the object compound were combined and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give object compound (26) (26 mg).

IR (KBr): 3365.2, 1751.0, 1727.9, 1635.3, 1259.3 cm^{-1}

25 NMR (DMSO- d_6 , δ): 0.96 (3H, d, J=6.6Hz), 1.12 (3H, d, J=5.8Hz), 1.2-2.6 (17H, m), 2.04 (3H, s), 2.8-3.4 (7H, m), 3.21 (3H, s), 3.6-5.3 (26H, m), 5.61 (2H, s), 6.70 (1H, d, J=8.2Hz), 6.77 (1H, d, J=8.2Hz), 6.96 (1H, s), 7.13 (2H, d, J=8.6Hz), 7.25-7.8 (4H, m), 7.93 (2H, d, J=8.6Hz), 8.09 (4H, s), 8.73 (1H, s), 8.80 (1H, d, J=6.7Hz)
30

ESI MASS (m/z): 1413 (M^+ -Na)

Example 27

A solution of 4-piperidone hydrochloride hydrate (28.4 mg) and succinic anhydride (18.5 mg) in DMF (2 ml) was

treated with diisopropylethylamine (23.9 mg) and aged for 3 hours at room temperature. To the resulting solution was added methanol (3 ml), DMF (1 ml), and after 30 minutes, acetic acid (27.7 mg), starting compound (31) (200 mg), and finally, sodium cyanoborohydride (12.6 mg). After 3 days at room temperature, ethyl acetate was added and the precipitate was collected, washed with ethyl acetate and dried. This solid was purified by ODS column chromatography (acetonitrile-water) to give object compound (27) (164 mg) as a white amorphous powder.

NMR (DMSO- d_6 + D $_2$ O, δ): 0.96 (3H, d, J=6.6Hz), 1.12 (3H, d, J=5.6Hz), 1.2-4.9 (54H, complex m), 3.21 (3H, s), 3.31 (2H, t, J=6.4H), 6.7-6.8 (2H, m), 6.99 (1H, br s), 7.13 (2H, d, J=8.9H), 7.97 (2H, d, J=8.9Hz), 8.08 (4H, ABq, J=8.6Hz, separation of inner lines = 6.6Hz)

MASS (m/z): 1528.3 (M^+ +Na)

Elemental Analysis Calcd. for C $_{67}$ H $_{90}$ N $_{11}$ O $_{23}$ S $_2$ Na \cdot 8H $_2$ O:

C 48.81, H 6.48, N 9.34

Found: C 48.84, H 6.46, N 9.29

Example 28

To a solution of the starting compound (28) (200 mg) and molecular sieves (4A) (200 mg) in N,N-dimethylformamide (4 ml) was added methyl iodide (1 ml), and stirred for 4 days at ambient temperature. The reaction mixture was filtrated, and the filtrate was diluted in water, and subjected to column chromatography on ODS (YMC-gel-ODS-AM-S-50 (Trademark: prepared by Yamamura Chemical Lab.)) eluting with 20% acetonitrile aqueous solution. The fractions containing the object compound were combined and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give the object compound (28) (46 mg).

IR (KBr): 3355, 2935, 1664, 1627, 1446, 1405, 1375,
1257, 1178, 1083, 1047 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ): 0.96 (3H, d, $J=6.8\text{Hz}$), 1.03 (3H, d,
5 $J=6.2\text{Hz}$), 1.2-1.6 (8H, m), 1.6-2.6 (15H, m), 2.6-
3.8 (6H, m), 3.09 (9H, s), 3.21 (3H, s), 3.30 (4H,
t, $J=6.4\text{Hz}$), 3.8-4.2 (7H, m), 4.2-4.6 (4H, m), 4.6-
5.0 (2H, m), 5.28 (2H, m), 5.75 (1H, m), 6.69 (1H,
d, $J=8.2\text{Hz}$), 6.80 (1H, d, $J=8.2\text{Hz}$), 6.92 (1H, s),
7.14 (2H, d, $J=8.8\text{Hz}$), 7.35 (1H, d, $J=7.4\text{Hz}$), 7.5
10 (1H, m), 7.86 (1H, m), 7.97 (2H, d, $J=8.8\text{Hz}$), 8.09
(4H, s), 8.32 (1H, s), 8.76 (1H, d, $J=6.8\text{Hz}$), 8.95
(1H, s)

MASS (m/z): 1363.4 ($M^+ + \text{Na}$)

15 Example 29

To a solution of starting compound (29) (0.2 g) and
ethyl bromoacetate (0.02 ml) in dimethylformamide (2 ml) was
added potassium carbonate (30.8 mg) and stirred for 24 hours
at ambient temperature. The reaction mixture was pulverized
20 with ethyl acetate. The precipitate was collected by
filtration and dried under reduced pressure. The powder was
added to 1N NaOH aq. (5 ml) and stirred for 1 hour at ambient
temperature. The reaction mixture was adjusted to pH 7 and
subjected to column chromatography on ODS (YMC-gel ODS-AM-S-
25 50) (Trademark: prepared by Yamamura Chemical Lab.) and
eluted with 30% acetonitrile aq. The fractions containing
the object compound were combined and evaporated under
reduced pressure to remove acetonitrile. The residue was
lyophilized to give object compound (29) (76 mg).

30 IR (KBr): 3353.6, 1631.5, 1444.4, 1257.4 cm^{-1}

ESI-MASS (m/z): 1355 ($M^+ - 1$)

Example 30

To a solution of starting compound (30) (0.1 g) and
35 ethyl bromoacetate (0.02 ml) in dimethylformamide (1 ml) was

added diisopropylethylamine (0.08 ml) and stirred for 24 hours at ambient temperature. The reaction mixture was pulverized with ethyl acetate. The precipitate was collected by filtration and dried under reduced pressure. The powder
5 was added to 1N NaOH aq. (5 ml) and stirred for 1 hour at ambient temperature. The reaction mixture was adjusted to pH 7 and subjected to column chromatography on ODS (YMC-gel ODS-AM-S-50) (Trademark: prepared by Yamamura Chemical Lab.) and eluted with 30% acetonitrile aq. The fractions containing
10 the object compound were combined and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give object compound (30) (48 mg).

IR (KBr): 3357.5, 1633.4, 1444.4, 1257.4 cm^{-1}

ESI-MASS (m/z): 1435 ($M^+ + Na$)

Example 31

A mixture of 4-[5-[4-[7-(cis-2,6-dimethylmorpholin-4-yl)heptyloxy]phenyl]isoxazol-3-yl]benzoic acid (100 mg), 1-hydroxybenzotriazole (41 mg) and 1-ethyl-3-(3'-
20 dimethylaminopropyl)carbodiimide hydrochloride (46.7 mg) in N,N-dimethylformamide (2 ml) was stirred for 30 minutes at ambient temperature. To the reaction mixture was added N,N-diisopropylethylamine (53.1 μl) and stirred for 40 minutes, then starting compound (31) (246.6 mg) was added and the
25 mixture was stirred for 4 hours. To the reaction mixture was added ethyl acetate (50 ml). The resulting precipitate was collected by filtration and washed with diisopropyl ether to give a crude light-brown powder (400.3 mg). The crude powder was purified by column chromatography on ODS (YMC-gel ODS-AM-S-50 (Trademark: prepared by YMC CO., Ltd.)) (35%
30 acetonitrile aqueous solution). The fractions containing the object compound were combined, and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give object compound (31).

IR (KBr): 3372.9, 1666.2, 1648.8, 1631.5, 1538.9,
1508.9, 1452.1, 1436.7, 1257.4 cm^{-1}

MASS (m/z): 1447.6 (M^{-1})

Elemental Analysis Calcd. for $\text{C}_{68}\text{H}_{92}\text{N}_{10}\text{O}_{23}\text{S}_7\text{H}_2\text{O}$:

C 51.83, H 6.78, N 8.89

Found: C 52.10, H 6.67, N 8.91

Example 32

To a solution of starting compound (32) (0.1 g) and 1-ethoxy-1-imino-3-methoxypropane (38.7 mg) in dimethylformamide (1 ml) was added diisopropylethylamine (0.067 ml) and stirred for 20 hours at ambient temperature. The reaction mixture was pulverized with ethyl acetate. The precipitate was collected by filtration and dried under reduced pressure. The powder was added to pH 6.86 buffer and subjected to column chromatography on ODS (YMC-gel ODS-AM-S-50) (Trademark: prepared by Yamamura Chemical Lab.) and eluted with 5-50% acetonitrile aq. The fractions containing the object compound were combined and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give object compound (32) (42 mg).

IR (KBr): 3353.6, 1635.3, 1257.4 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ): 0.98 (3H, d, $J=6.6\text{Hz}$), 1.13 (3H, d, $J=5.8\text{Hz}$), 1.2-2.6 (19H, m), 2.8-3.4 (9H, m), 3.21 (3H, s), 3.6-5.3 (26H, m), 6.71 (1H, d, $J=8.2\text{Hz}$), 6.77 (1H, d, $J=8.2\text{Hz}$), 7.00 (1H, s), 7.13 (2H, d, $J=8.6\text{Hz}$), 7.25-7.8 (3H, m), 7.96 (2H, d, $J=8.6\text{Hz}$), 8.05 (2H, d, $J=8.9\text{Hz}$), 8.11 (2H, d, $J=8.9\text{Hz}$), 8.70 (1H, s), 8.85 (1H, d, $J=6.7\text{Hz}$)

MASS (m/z): 1383 (M^{+1})

Elemental Analysis Calcd. for $\text{C}_{62}\text{H}_{85}\text{N}_{11}\text{O}_{21}\text{S}_2\text{H}_2\text{O}$:

C 48.71, H 6.66, N 10.08

Found: C 48.50, H 6.50, N 9.96

Example 33

To a solution of starting compound (33) (0.1 g) and 2-carbamoyl-1-ethoxy-1-iminopropane (38.5 mg) in dimethylformamide (1 ml) was added diisopropylethylamine (0.067 ml) and stirred for 20 hours at ambient temperature. The reaction mixture was pulverized with ethyl acetate. The precipitate was collected by filtration and dried under reduced pressure. The powder was added to pH 6.86 buffer and subjected to column chromatography on ODS (YMC-gel ODS-AM-S-50) (Trademark: prepared by Yamamura Chemical Lab.) and eluted with 5-50% acetonitrile aq. The fractions containing the object compound were combined and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give object compound (33) (48 mg).

IR (KBr): 1658.5, 1635.3, 1257.4 cm^{-1}

NMR (DMSO- d_6 , δ): 0.98 (3H, d, $J=6.6\text{Hz}$), 1.13 (3H, d, $J=5.8\text{Hz}$), 1.2-2.6 (17H, m), 2.8-3.4 (7H, m), 3.21 (3H, s), 3.6-5.3 (28H, m), 6.71 (1H, d, $J=8.2\text{Hz}$), 6.77 (1H, d, $J=8.2\text{Hz}$), 7.00 (1H, s), 7.13 (2H, d, $J=8.6\text{Hz}$), 7.32 (1H, s), 7.25-7.8 (4H, m), 7.96 (2H, d, $J=8.6\text{Hz}$), 8.05 (2H, d, $J=8.9\text{Hz}$), 8.11 (2H, d, $J=8.9\text{Hz}$), 8.70 (1H, s), 8.85 (1H, d, $J=6.7\text{Hz}$)

ESI-MASS (m/z): 1382 (M^+-1)

Elemental Analysis Calcd. for $\text{C}_{61}\text{H}_{82}\text{N}_{12}\text{O}_{21}\text{S}_2 \cdot 7\text{H}_2\text{O}$:

C 48.53, H 6.41, N 11.13

Found: C 48.50, H 6.39, N 10.92

Example 34

A mixture of starting compound (34) (50 mg), N,N-diisopropylethylamine (6.70 μl) and zeolite synthetic A-4 powder (50 mg) in N,N-dimethylformamide (0.5 ml) was stirred for 30 minutes at ambient temperature. To the mixture was added acetic anhydride (3.63 μl) and stirred for 2 hours. The zeolite synthetic A-4 powder was filtered off, and to the filtrate was added ethyl acetate (100 ml). The resulting

precipitate was collected by filtration and washed with diisopropyl ether to give a crude white powder (48.7 mg). The crude powder was purified by column chromatography on ODS (YMC-gel ODS-AM-S-50 (Trademark: prepared by YMC Co., Ltd.)) (25% acetonitrile aqueous solution). The fractions containing the object compound were combined, and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give object compound (34) (31.5 mg).

IR (KBr): 3353.6, 1658.5, 1635.3, 1546.6, 1531.2, 1517.7, 1444.4, 1259.3 cm^{-1}

NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.7\text{Hz}$), 1.14 (3H, d, $J=5.9\text{Hz}$), 1.2-5.5 (55H, m), 6.71 (1H, d, $J=8.1\text{Hz}$), 6.7-6.9 (1H, m), 6.96 (1H, d, $J=1.6\text{Hz}$), 7.13 (2H, d, $J=8.9\text{Hz}$), 7.3-7.8 (4H, m), 7.97 (2H, d, $J=8.8\text{Hz}$), 7.9-9.0 (7H, m)

MASS (m/z): 1339.3 (M^- -Na)

Elemental Analysis Calcd. for $\text{C}_{60}\text{H}_{79}\text{N}_{10}\text{NaO}_{21}\text{S}_3 \cdot 10\text{H}_2\text{O}$:

C 46.69, H 6.46, N 9.07

Found: C 46.46, H 6.11, N 8.95

Example 35

A solution of starting compound (35) (500 mg) in water (20 ml) and 1N-sodium hydroxide (1.15 μl) was treated dropwise with a solution of allyloxycarbonyl chloride (49 μl) in tetrahydrofuran (1 ml). After 1 hour, the solution was diluted with water and purified by ODS column chromatography eluting with acetonitrile-water mixtures. Product-containing fractions were pooled, evaporated to remove organic solvent and lyophilized to give object compound (35) (350 mg) as a white amorphous powder.

IR (KBr): 2935, 1664, 1633, 1610, 1527, 1442.5, 1412, 1383, 1348, 1257, 1178, 1113, 1088, 1045 cm^{-1}

NMR (DMSO- d_6 + D_2O , δ): 0.97 (3H, d, $J=6.7\text{Hz}$), 1.11 (3H, d, $J=5.8\text{Hz}$), 1.2-5.1 (53H, complex m), 3.21 (3H, s), 3.31 (2H, t, $J=6.4\text{Hz}$), 5.12-5.29 (2H, m), 5.8-

6.0 (1H, m), 6.70-6.80 (2H, m), 6.99 (1H, br s),
7.14 (2H, d, J=8.8Hz), 7.98 (2H, d, J=8.8Hz), 8.09
(4H, s)

MASS (m/z): 1381.3 (M^+ -Na)

5 Elemental Analysis Calcd. for $C_{62}H_{81}N_{10}O_{22}S_2Na \cdot 5H_2O$:
C 49.79, H 6.13, N 9.37
Found: C 49.79, H 6.07, N 9.30

Example 36

10 To a solution of starting compound (36) (100 mg) in N,N-
dimethylformamide (1 ml) was added sulfur trioxide pyridine
complex (61.2 mg) and stirred for 2 days at ambient
temperature. To the reaction mixture was added ethyl acetate
(30 ml), and the resulting precipitate was collected by
15 filtration and washed with diisopropyl ether to give a crude
white powder. The crude powder was purified by column
chromatography on ODS (YMC-gel ODS-AM-S-50 (Trademark:
prepared by YMC Co., Ltd.)) (20% acetonitrile aqueous
solution). The fractions containing the object compound were
20 combined, and evaporated under reduced pressure to remove
acetonitrile. The residue was lyophilized to give object
compound (36) (12.7 mg).

IR (KBr): 3446.2, 1648.8, 1633.4, 1540.8, 1515.8,
1450.2, 1442.5, 1257.4 cm^{-1}

25 NMR (DMSO- d_6 , δ): 0.96 (3H, d, J=6.5Hz), 1.0-5.4 (56H,
m), 6.6-6.8 (2H, m), 6.9-7.1 (1H, m), 7.13 (2H, d,
J=8.8Hz), 7.97 (2H, d, J=8.8Hz), 8.08 (4H, s), 7.3-
9.0 (7H, m)

MASS (m/z): 1399.3 (M^- -1)

Example 37

A mixture of starting compound (37) (100 mg), N,N-
diisopropylethylamine (14.7 μ l), zeolite synthetic A-4 powder
(400 mg) and N,N-dimethylformamide dimethyl acetal (15.3 μ l)
35 in N,N-dimethylformamide (1 ml) was stirred for 40 minutes at

ambient temperature. To the reaction mixture was added N,N-diisopropylethylamine (1.5 μ l) and N,N-dimethylformamide dimethyl acetal (1.5 μ l), the mixture was stirred for 1 hour at ambient temperature, and ethyl acetate (50 ml) was added, and the resulting precipitate was collected by filtration and washed with diisopropyl ether to give a crude white powder (72.2 mg). The crude powder was purified by column chromatography on ODS (YMC-gel ODS-AM-S-50 (Trademark: prepared by YMC Co., Ltd.)) (40% acetonitrile aqueous solution). The fractions containing the object compound were combined, and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give object compound (37) (27.9 mg).

IR (KBr): 3359.4, 1710.6, 1648.8, 1631.5, 1538.9, 1513.8, 1442.5, 1257.4 cm^{-1}

NMR (DMSO-d_6 , δ): 0.97 (3H, d, $J=6.8\text{Hz}$), 1.0-5.4 (62H, m), 6.6-6.9 (2H, m), 6.99 (1H, s), 7.14 (2H, d, $J=8.8\text{Hz}$), 7.3-7.9 (3H, m), 7.97 (2H, d, $J=8.8\text{Hz}$), 8.0-8.2 (4H, m), 8.3-9.2 (4H, m)

MASS (m/z): 1352.5 (M^{-1})

Elemental Analysis Calcd. for $\text{C}_{61}\text{H}_{83}\text{N}_{11}\text{O}_{20}\text{S}_2 \cdot 6\text{H}_2\text{O}$:

C 49.02, H 6.41, N 10.31

Found: C 49.20, H 6.35, N 10.27

25 Example 38

To a solution of the starting compound (38) (100 mg) in N,N-dimethylformamide (1 ml) was added S,S'-dimethyl N-cyanodithioiminocarbonate (113 mg) and diisopropyl ethyl amine (0.2 ml), and stirred for 2 hours at ambient temperature. The reaction mixture was pulverized with ethyl acetate and washed by diisopropyl ether. The precipitate was filtered and dried to give the object compound (38) (111 mg).

NMR (DMSO-d_6 , δ): 0.97 (3H, d, $J=6.7\text{Hz}$), 1.0-1.6 (14H, m), 1.6-3.9 (25H, m), 3.21 (3H, s), 3.9-4.3 (7H, m), 4.43 (2H, m), 4.5-4.7 (2H, m), 4.88 (2H, d,

J=5.7Hz), 5.0-5.3 (4H, m), 6.71 (1H, d, J=8.2Hz),
6.78 (1H, d, J=8.2Hz), 6.97 (1H, s), 7.13 (2H, d,
J=8.8Hz), 7.50 (1H, d, J=8.5Hz), 7.63 (1H, m), 7.7
(1H, m), 7.97 (2H, d, J=8.8Hz), 8.09 (4H, s), 8.12
(1H, m), 8.71 (1H, s), 8.78 (1H, d, J=6.4Hz)

MASS (m/z): 1395.3 ($M^+ - 1$)

Example 39

To a solution of the starting compound (39) (96 mg) in
water (1 ml) was added a solution of ammonia in methanol (1
ml), and stirred for 2 days at ambient temperature. The
reaction mixture was diluted in water, and subjected to
column chromatography on ODS (YMC-gel ODS-AM-S-50 (Trademark:
prepared by Yamamura Chemical Lab.)) eluting with 20%
acetonitrile aqueous solution. The fractions containing the
object compound were combined, and evaporated under reduced
pressure to remove acetonitrile. The residue was lyophilized
to give the object compound (39) (39 mg).

IR (KBr): 3351, 2935, 1635, 1567, 1533, 1517, 1444,
1415, 1257, 1178, 1087, 1047 cm^{-1}

NMR (DMSO- d_6 , δ): 0.98 (3H, d, J=6.7Hz), 1.13 (3H, d,
J=5.7Hz), 1.2-1.6 (11H, m), 1.6-2.6 (10H, m), 2.90
(1H, m), 3.20 (1H, m), 3.21 (3H, s), 3.30 (4H, t,
J=6.4Hz), 3.3-4.6 (14H, m), 4.6-4.8 (2H, m), 4.87
(1H, d, J=5.7Hz), 5.06 (1H, d, J=7.2Hz), 5.2 (4H,
m), 6.71 (1H, d, J=8.2Hz), 6.78 (1H, d, J=8.2Hz),
6.7 (3H, m), 6.97 (1H, s), 7.13 (2H, d, J=8.8Hz),
7.46 (1H, d, J=8.8Hz), 7.65 (2H, m), 7.97 (2H, d,
J=8.8Hz), 8.09 (4H, s), 8.13 (1H, m), 8.71 (1H, s),
8.84 (1H, d, J=7.7Hz)

MASS (m/z): 1364.4 ($M^+ - \text{Na}$)

Elemental Analysis Calcd. for $\text{C}_{60}\text{H}_{78}\text{N}_{13}\text{NaO}_{20}\text{S}_2 \cdot 8\text{H}_2\text{O}$:

C 47.02, H 6.18, N 11.88

Found: C 47.15, H 5.89, N 11.82

Example 40

To a solution of the starting compound (40) (100 mg) in acetonitrile (1 ml) and water (1 ml) was added formaline (35% aqueous) (67 μ l), and stirred for 30 minutes at ambient temperature. To a solution of the reaction mixture was added sodium cyanoborohydride (48 mg) and stirred for 5 hours. The reaction mixture was diluted in water, and subjected to column chromatography on ODS (YMC-gel ODS-AM-S-50 (Trademark: prepared by Yamamura Chemical Lab.)) eluting with 20% acetonitrile aqueous solution. The fractions containing the object compound were combined, and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give the object compound (40) (27 mg).

IR (KBr): 3355, 2937, 1658, 1633, 1533, 1517, 1444, 1257, 1178, 1087, 1045 cm^{-1}

NMR (DMSO- d_6 , δ): 0.95 (3H, d, $J=6.7\text{Hz}$), 1.10 (3H, d, $J=5.7\text{Hz}$), 1.3-2.6 (30H, m), 2.6-3.0 (4H, m), 3.21 (3H, s), 3.0-4.1 (11H, m), 4.22 (2H, m), 4.4 (4H, m), 4.80 (3H, m), 4.9 (2H, m), 5.17 (2H, m), 5.24 (1H, d, $J=5.7\text{Hz}$), 6.69 (1H, d, $J=8.2\text{Hz}$), 6.76 (1H, d, $J=8.2\text{Hz}$), 6.99 (1H, s), 7.05 (1H, s), 7.14 (2H, d, $J=8.8\text{Hz}$), 7.41 (2H, d, $J=9.1\text{Hz}$), 7.85 (1H, m), 7.97 (2H, d, $J=8.8\text{Hz}$), 8.10 (4H, s), 8.70 (1H, m), 8.72 (1H, s), 8.87 (1H, m)

MASS (m/z): 1365.4 (M^+-1)

Elemental Analysis Calcd. for $\text{C}_{63}\text{H}_{86}\text{N}_{10}\text{O}_{20}\text{S}_2 \cdot 8\text{H}_2\text{O}$:

C 50.06, H 6.80, N 9.27

Found: C 49.95, H 6.38, N 9.21

Example 41

To a solution of the starting compound (41) (100 mg) and potassium carbonate (53 mg) in N,N-dimethylformamide (1 ml) was added 1,5-dibromopentane (13 μ l), and stirred for 3 days at ambient temperature. The reaction mixture was filtrated, and the filtrate was diluted in water, and subjected to

column chromatography on ODS (YMC-gel ODS-AM-S-50 (Trademark: prepared by Yamamura Chemical Lab.)) eluting with 20% acetonitrile aqueous solution. The fractions containing the object compound were combined, and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give the object compound (41) (38 mg).

IR (KBr): 3353, 2935, 1658, 1635, 1546, 1529, 1517, 1444, 1257, 1083, 1047 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ): 0.98 (3H, d, $J=6.7\text{Hz}$), 1.09 (3H, d, $J=5.7\text{Hz}$), 1.3-1.6 (8H, m), 1.6-2.4 (15H, m), 2.4-3.0 (6H, m), 3.21 (3H, s), 3.0-4.2 (11H, m), 4.23 (2H, m), 4.43 (4H, m), 4.80 (3H, m), 4.95 (2H, d, $J=6.2\text{Hz}$), 5.1-5.3 (3H, m), 6.70 (1H, d, $J=8.2\text{Hz}$), 6.77 (1H, d, $J=8.2\text{Hz}$), 6.99 (1H, s), 7.14 (2H, d, $J=8.8\text{Hz}$), 7.43 (2H, m), 7.83 (1H, d, $J=7.2\text{Hz}$), 7.97 (2H, d, $J=8.8\text{Hz}$), 8.10 (4H, s), 8.60 (1H, m), 8.71 (1H, s), 8.87 (1H, d, $J=7.2\text{Hz}$)

MASS (m/z): 1325.4 (M^+-1)

Elemental Analysis Calcd. for $\text{C}_{60}\text{H}_{92}\text{N}_{10}\text{O}_{20}\text{S}_2\cdot 8\text{H}_2\text{O}$:

C 48.97, H 6.71, N 9.52

Found: C 48.97, H 6.32, N 9.63

Example 42

To a solution of the starting compound (42) (200 mg) and molecular sieves (4A) (200 mg) in N,N -dimethylformamide (4 ml) was added cyanogen bromide (80 mg), and stirred for 5 hours at ambient temperature. The reaction mixture was filtrated, and the filtrate was diluted in water, and subjected to column chromatography on ODS (YMC-gel-ODS-AM-S-50 (Trademark: prepared by Yamamura Chemical Lab.)) eluting with 20% acetonitrile aqueous solution. The fractions containing the object compound were combined, and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give the object compound (42) (3.8 mg).

NMR ($\text{DMSO}-d_6$, δ): 0.97 (3H, d, $J=6.7\text{Hz}$), 1.13 (3H, d,

J=5.7Hz), 1.2-1.6 (8H, m), 1.6-4.5 (30H, m), 2.79 (3H, s), 3.21 (3H, s), 4.7 (2H, m), 4.85 (2H, d, J=6.0Hz), 5.07 (2H, m), 5.2 (3H, m), 6.69 (2H, m), 6.95 (1H, s), 7.14 (2H, d, J=8.8Hz), 7.46 (1H, m), 7.64 (2H, m), 7.97 (2H, d, J=8.8Hz), 8.09 (4H, s), 8.07 (1H, d, J=7.8Hz), 8.57 (1H, d, J=7.8Hz), 8.27 (1H, m), 8.68 (1H, m), 8.72 (1H, s)

MASS (m/z): 1336.3 (M^+-1)

10 Example 43

A solution of starting compound (43) (100 mg) in N,N-dimethylformamide (2 ml) was treated with 1,1'-carbonyldiimidazole (16.2 mg) and diisopropylethylamine (10.9 mg). After 20 hours, a further 3.7 mg of 1,1'-carbonyldiimidazole was added. After a further 1 hour, the mixture was diluted with water and purified by ODS column chromatography eluting with acetonitrile-water mixtures and product-containing fractions lyophilized to afford 80.8 mg of object compound (43) as a white amorphous powder.

IR (KBr): 2935, 2864, 1658.5, 1637, 1529, 1518, 1444, 1257 cm^{-1}

NMR (DMSO- d_6 + D_2O , δ): 0.93-1.07 (6H, m), 1.20-4.5 (37H, m), 3.21 (3H, s), 3.31 (2H, t, J=6.4Hz), 4.07 (2H, t, J=6.3Hz), 4.81 (1H, m), 4.99 (1H, d, J=4Hz), 6.71 (1H, d, J=8.2Hz), 6.78-6.83 (1H, m), 6.98 (1H, d, J=1.7Hz), 7.13 (2H, d, J=8.9Hz), 7.97 (2H, d, J=8.9Hz), 8.02-8.13 (4H, m)

MASS (m/z): 1323.2 (M^+-Na)

Elemental Analysis Calcd. for $C_{59}H_{75}N_{10}O_{21}S_2N_9 \cdot 6H_2O$:

C 48.39, H 6.06, N 9.56

Found: C 48.37, H 6.00, N 9.61

The following compound was obtained according to a similar manner to that of Example 43.

Example 44

IR (KBr): 3352, 2935, 2864, 1635, 1547, 1516, 1444,
1255, 1174, 1045 cm^{-1}

NMR (DMSO-d_6 + D_2O , δ): 0.95 (3H, d, $J=6.9\text{Hz}$), 1.03 (3H,
d, $J=5.9\text{Hz}$), 1.20-5.12 (39H, m), 3.21 (3H, s), 3.31
(2H, t, $J=6.4\text{Hz}$), 4.07 (2H, t, $J=6.1\text{Hz}$), 6.72 (1H,
d, $J=8.2\text{Hz}$), 6.82 (1H, dd, $J=8.2$, 1.7Hz), 6.99 (1H,
d, $J=1.7\text{Hz}$), 7.13 (2H, d, $J=8.9\text{Hz}$), 7.98 (2H, d,
 $J=8.9\text{Hz}$), 8.08 (4H, m)

MASS (m/z): 1339.2 (M^+-Na)

Elemental Analysis Calcd. for $\text{C}_{59}\text{H}_{75}\text{N}_{10}\text{O}_{20}\text{S}_3\text{Na}\cdot 6\text{H}_2\text{O}$:

C 48.16, H 5.96, N 9.52

Found: C 48.01, H 5.74, N 9.43

Example 45

A mixture of starting compound (45) (220 mg) and 1N
sodium hydroxide aqueous solution (30 ml) was stirred for 1
hour at ambient temperature. The reaction mixture was
adjusted to pH 9 with 1N hydrochloric acid, and purified by
column chromatography on ODS (YMC-gel ODS-AM-S-50 (Trademark:
prepared by YMC Co., Ltd.)) (20% acetonitrile aqueous
solution). The fractions containing the object compound were
combined, and evaporated under reduced pressure to remove
acetonitrile. The residue was lyophilized to give object
compound (45).

IR (KBr): 3382.5, 1658.5, 1635.3, 1444.4, 1257.4,
1087.7, 1045.2 cm^{-1}

NMR (DMSO-d_6 , δ): 0.97 (3H, d, $J=6.9\text{Hz}$), 1.11 (3H, d,
 $J=5.0\text{Hz}$), 1.2-5.4 (64H, m), 6.68 (1H, d, $J=8.1\text{Hz}$),
6.78 (1H, d, $J=8.0\text{Hz}$), 6.92 (1H, d, $J=1.8\text{Hz}$), 7.13
(2H, d, $J=8.9\text{Hz}$), 7.97 (2H, d, $J=8.8\text{Hz}$), 8.07 (4H,
s), 7.3-9.0 (6H, m)

MASS (m/z): 1411.4 (M^+-Na)

The following compounds were obtained according to a

similar manner to that of Example 45.

Example 46

major object compound (46)

IR (KBr): 3353.6, 1658.5, 1635.3, 1546.6, 1529.3,
1517.7, 1444.4, 1257.4 cm^{-1}

NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.7\text{Hz}$), 1.10 (3H, d,
 $J=5.3\text{Hz}$), 1.2-5.4 (70H, m), 6.68 (1H, d, $J=8.2\text{Hz}$),
6.76 (1H, d, $J=9.7\text{Hz}$), 6.92 (1H, s), 7.13 (2H, d,
 $J=8.8\text{Hz}$), 7.97 (2H, d, $J=8.7\text{Hz}$), 8.04 (2H, d,
 $J=9.3\text{Hz}$), 8.10 (2H, d, $J=9.0\text{Hz}$), 7.3-9.0 (6H, m)

MASS (m/z): 1453.4 (M^- -Na)

Elemental Analysis Calcd. for $\text{C}_{67}\text{H}_{93}\text{N}_{10}\text{NaO}_{22}\text{S}_2\cdot 9\text{H}_2\text{O}$:

C 49.08, H 6.82, N 8.54

Found: C 49.20, H 6.72, N 8.56

minor object compound (46)

IR (KBr): 3353.6, 1658.5, 1635.3, 1567.8, 1550.5,
1533.1, 1517.7, 1444.4, 1407.8, 1257.4 cm^{-1}

NMR (DMSO- d_6 , δ): 0.96 (3H, d, $J=6.6\text{Hz}$), 1.1-5.4 (88H,
m), 6.70 (1H, d, $J=8.2\text{Hz}$), 6.78 (1H, d, $J=9.8\text{Hz}$),
6.90 (1H, s), 7.13 (2H, d, $J=8.9\text{Hz}$), 7.97 (2H, d,
 $J=8.8\text{Hz}$), 8.07 (4H, s), 7.3-9.0 (6H, m)

MASS (m/z): 1631.4 (M^- -Na)

Elemental Analysis Calcd. for $\text{C}_{76}\text{H}_{108}\text{N}_{10}\text{Na}_2\text{O}_{24}\text{S}_2\cdot 11\text{H}_2\text{O}$:

C 49.24, H 7.07, N 7.55

Found: C 49.22, H 6.93, N 7.57

Example 47

deleted

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deleted

10

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Example 48

20 A mixture of starting compound (48) (100 mg), N,N-diisopropylethylamine (13.4 μ l) and zeolite synthetic A-4 powder (100 mg) in N,N-dimethylformamide (1 ml) was stirred for 30 minutes at ambient temperature. The mixture was cooled to 0°C and treated with methanesulfonyl chloride (6 μ l) and stirred for 30 minutes at ambient temperature. The
25 mixture was then treated with further methanesulfonyl chloride (6 μ l) and stirred for 30 minutes at ambient temperature. To the mixture was added N,N-diisopropylethylamine (13.4 μ l) and stirred for 15 minutes at ambient temperature. The mixture was treated with
30 methanesulfonyl chloride (6 μ l) and stirred for 30 minutes at ambient temperature. To the mixture was added N,N-diisopropylethylamine (13.4 μ l) and stirred for 15 minutes at ambient temperature. The zeolite synthetic A-4 powder was filtered off, and to the filtrate was added ethyl acetate
35 (100 ml). The resulting precipitate was collected by

filtration and washed with diisopropyl ether to give a crude powder. The crude powder was purified by column chromatography on ODS (YMC-gel ODS-AM-S-50 (Trademark: prepared by YMC Co., Ltd.)) (25% acetonitrile aqueous solution). The fractions containing the object compound were combined, and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give object compound (48) (30.0 mg).

IR (KBr): 3430.7, 1658.5, 1635.3, 1444.4, 1259.3 cm^{-1}

NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.7\text{Hz}$), 1.14 (3H, d, $J=5.9\text{Hz}$), 1.2-5.5 (55H, m), 6.6-6.9 (3H, m), 6.97 (1H, d, $J=1.6\text{Hz}$), 7.13 (2H, d, $J=8.9\text{Hz}$), 7.3-7.8 (3H, m), 7.97 (2H, d, $J=8.8\text{Hz}$), 8.09 (4H, s), 8.0-9.0 (3H, m)

MASS (m/z): 1375.3 (M^- -Na)

Elemental Analysis Calcd. for $\text{C}_{59}\text{H}_{79}\text{N}_{10}\text{NaO}_{22}\text{S}_3\cdot 7\text{H}_2\text{O}$:

C 46.45, H 6.14, N 9.18

Found: C 46.26, H 6.11, N 9.01

The following compounds [Examples 49 to 52] were obtained according to a similar manner to that of Example 48.

Example 49

IR (KBr): 3380.6, 1666.2, 1648.8, 1631.5, 1538.9, 1513.8, 1450.2, 1450.2, 1261.2 cm^{-1}

NMR (DMSO- d_6 , δ): 0.96 (3H, d, $J=6.6\text{Hz}$), 1.16 (3H, d, $J=5.9\text{Hz}$), 1.2-5.5 (60H, m), 6.4-6.6 (1H, m), 6.71 (1H, d, $J=8.1\text{Hz}$), 6.78 (1H, d, $J=9.8\text{Hz}$), 6.96 (1H, s), 7.13 (2H, d, $J=8.8\text{Hz}$), 7.3-8.2 (4H, m), 7.93 (2H, d, $J=8.6\text{Hz}$), 8.05 (2H, d, $J=9.0\text{Hz}$), 8.11 (2H, d, $J=8.9\text{Hz}$), 8.5-9.0 (2H, m)

MASS (m/z): 1410.4 (M^- -Na)

Elemental Analysis Calcd. for $\text{C}_{63}\text{H}_{84}\text{N}_{11}\text{NaO}_{22}\text{S}_2\cdot 8\text{H}_2\text{O}$:

C 47.93, H 6.38, N 9.76

Found: C 48.05, H 6.25, N 9.56

Example 50

IR (KBr): 3363.2, 1666.2, 1648.8, 1631.5, 1540.8,
1513.8, 1450.2, 1442.5, 1257.4 cm^{-1}

NMR (DMSO- d_6 , δ): 0.96 (3H, d, $J=6.6\text{Hz}$), 1.16 (3H, d,
 $J=5.9\text{Hz}$), 1.2-5.5 (58H, m), 6.1-6.3 (1H, m), 6.71
(1H, d, $J=18.1\text{Hz}$), 6.78 (1H, d, $J=10.0\text{Hz}$), 6.96
(1H, s), 7.13 (2H, d, $J=8.8\text{Hz}$), 7.4-7.9 (4H, m),
7.97 (2H, d, $J=8.7\text{Hz}$), 8.06 (2H, d, $J=10.4\text{Hz}$), 8.11
(2H, d, $J=9.0\text{Hz}$), 8.6-8.8 (2H, m)

MASS (m/z): 1368.4 ($\text{M}^- - \text{Na}$)

Elemental Analysis Calcd. for $\text{C}_{61}\text{H}_{82}\text{N}_{11}\text{NaO}_{21}\text{S}_2 \cdot 9\text{H}_2\text{O}$:

C 47.13, H 6.48, N 9.91

Found: C 47.36, H 6.24, N 9.86

Example 51

IR (KBr): 3359.4, 1666.2, 1648.8, 1631.5, 1540.8,
1513.8, 1450.2, 1442.5, 1257.4 cm^{-1}

NMR (DMSO- d_6 , δ): 0.8-1.1 (9H, m), 1.17 (3H, d,
 $J=6.0\text{Hz}$), 1.2-5.5 (56H, m), 6.0-6.2 (1H, m), 6.71
(1H, d, $J=8.1\text{Hz}$), 6.7-6.9 (1H, m), 6.96 (1H, d,
 $J=1.6\text{Hz}$), 7.13 (2H, d, $J=8.9\text{Hz}$), 7.4-7.9 (4H, m),
7.97 (2H, d, $J=8.8\text{Hz}$), 8.05 (2H, d, $J=9.3\text{Hz}$), 8.10
(2H, d, $J=9.0\text{Hz}$), 8.6-8.8 (2H, m)

MASS (m/z): 1396.5 ($\text{M}^- - \text{Na}$)

Elemental Analysis Calcd. for $\text{C}_{63}\text{H}_{86}\text{N}_{11}\text{NaO}_{21}\text{S}_2 \cdot 8\text{H}_2\text{O}$:

C 48.36, H 6.57, N 9.85

Found: C 48.50, H 6.34, N 9.82

Example 52

IR (KBr): 3392.2, 1631.5, 1504.8, 1515.8, 1442.5,
1257.4 cm^{-1}

NMR (DMSO- d_6 , δ): 0.96 (3H, d, $J=6.6\text{Hz}$), 1.16 (3H, d,
 $J=5.7\text{Hz}$), 1.2-5.5 (60H, m), 5.9-6.1 (1H, m), 6.71
(1H, d, $J=8.1\text{Hz}$), 6.78 (1H, d, $J=10.0\text{Hz}$), 6.96 (1H,

s), 7.13 (2H, d, J=8.8Hz), 7.3-7.9 (4H, m), 7.97 (2H, d, J=8.8Hz), 8.0-8.2 (4H, m), 8.6-8.8 (2H, m)
MASS (m/z): 1394.4 (M⁻-Na)

5 Example 53

To a mixture of starting compound (53) (100 mg) and zeolite synthetic A-4 powder (100 mg) in N,N-dimethylformamide (1 ml) was added propane sultone (9.4 mg) and stirred for 3 days 7 hours at ambient temperature. To the reaction mixture was added ethyl acetate (20 ml). The resulting precipitate was collected by filtration and washed with diisopropyl ether to give a crude white powder (104.3 mg). The crude powder was purified by column chromatography on ODS (YMC-gel ODS-AM-S-50 (Trademark: prepared by YMC Co., Ltd.)) (20% acetonitrile aqueous solution). The fractions containing the object compound were combined, and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give object compound (53) (34.2 mg).

IR (KBr): 3372.9, 1658.5, 1635.3, 1546.6, 1529.3, 1517.7, 1444.4, 1255.4, 1178.3, 1045.2 cm⁻¹

NMR (DMSO-d₆, δ): 0.97 (3H, d, J=6.6Hz), 1.13 (3H, d, J=5.8Hz), 1.2-5.5 (60H, m), 6.71 (1H, d, J=8.2Hz), 6.77 (1H, d, J=10.0Hz), 6.95 (1H, s), 7.13 (2H, d, J=8.9Hz), 7.97 (2H, d, J=8.7Hz), 8.09 (4H, s), 7.3-9.0 (6H, m)

MASS (m/z): 1419.4 (M⁻-Na)

Elemental Analysis Calcd. for C₆₁H₈₃N₁₀NaO₂₃S₃·8H₂O:

C 46.15, H 6.28, N 8.82

Found: C 46.11, H 6.04, N 8.74

The following compounds [Examples 54 to 56] were obtained according to a similar manner to that of Example 53.

Example 54

IR (KBr): 3355.5, 2935.1, 1635.3, 1529.3, 1517.7,
1444.4, 1257.4, 1178.3, 1045.2 cm^{-1}

NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.8\text{Hz}$), 1.12 (3H, d,
 $J=5.3\text{Hz}$), 1.2-5.4 (62H, m), 6.71 (1H, d, $J=8.1\text{Hz}$),
6.78 (1H, d, $J=9.5\text{Hz}$), 6.96 (1H, s), 7.13 (2H, d,
 $J=8.8\text{Hz}$), 7.97 (2H, d, $J=8.7\text{Hz}$), 8.05 (2H, d,
 $J=8.8\text{Hz}$), 8.12 (2H, d, $J=8.5\text{Hz}$), 7.3-9.0 (6H, m)

MASS (m/z): 1455.3 (M^{-1})

Example 55

IR (KBr): 3369.0, 1633.4, 1533.1, 1517.7, 1444.4,
1413.6, 1257.4 cm^{-1}

NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.6\text{Hz}$), 1.14 (3H, d,
 $J=5.7\text{Hz}$), 1.2-5.4 (58H, m), 6.6-6.9 (2H, m), 6.94
(1H, s), 7.13 (2H, d, $J=8.9\text{Hz}$), 7.97 (2H, d,
 $J=8.8\text{Hz}$), 8.08 (4H, s), 7.3-9.0 (6H, m)

MASS (m/z): 1391.2 (M^{-1})

Elemental Analysis Calcd. for $\text{C}_{61}\text{H}_{81}\text{N}_{10}\text{NaO}_{22}\text{S}_2\cdot 8\text{H}_2\text{O}$:

C 47.65, H 6.36, N 9.11

Found: C 47.52, H 6.10, N 8.84

Example 56

IR (KBr): 3363.2, 1666.2, 1648.8, 1631.5, 1538.9,
1513.8, 1450.2, 1442.5, 1257.4 cm^{-1}

NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.6\text{Hz}$), 1.12 (3H, d,
 $J=5.6\text{Hz}$), 1.2-5.6 (60H, m), 6.71 (1H, d, $J=8.1\text{Hz}$),
6.77 (1H, d, $J=9.1\text{Hz}$), 6.97 (1H, s), 7.13 (2H, d,
 $J=8.8\text{Hz}$), 7.97 (2H, d, $J=8.7\text{Hz}$), 8.06 (2H, d,
 $J=8.6\text{Hz}$), 8.13 (2H, d, $J=8.7\text{Hz}$), 7.3-9.0 (6H, m)

MASS (m/z): 1457.4 (M^{-1})

Elemental Analysis Calcd. for $\text{C}_{61}\text{H}_{83}\text{N}_{10}\text{NaO}_{24}\text{S}_3\cdot 9\text{H}_2\text{O}$:

C 45.18, H 6.28, N 8.64

Found: C 45.14, H 6.11, N 8.52

The following compounds [Examples 57 to 58] were obtained according to a similar manner to that of Example 18.

Example 57

IR (KBr): 1670, 1632, 1535, 1518, 1443 cm^{-1}

NMR (DMSO- d_6 + D_2O , δ): 0.94 (3H, d, $J=6.70\text{Hz}$), 1.10 (3H, d, $J=5.86\text{Hz}$), 1.35 (9H, s), 1.45-1.95 (6H, m), 2.10-2.40 (2H, m), 2.80-3.45 (7H, m), 3.60-4.80 (15H, m), 5.05-5.40 (2H, m), 5.70-6.05 (1H, m), 6.74 (1H, d, $J=8.18\text{Hz}$), 6.82 (1H, d, $J=10.2\text{Hz}$), 7.06 (1H, s)

ESI MASS (m/z)(Positive): 1135.2 (M^+ +Na)

Elemental Analysis Calcd. for $C_{44}H_{65}N_8O_{22}SNa \cdot 4H_2O$:

C 44.59, H 6.21, N 9.45

Found: C 44.55, H 6.37, N 9.39

Example 58

IR (KBr): 3344, 2925.5, 2854, 1664, 1635, 1529, 1518, 1446, 1277, 1252, 1171, 1086, 1045 cm^{-1}

NMR (DMSO- d_6 + D_2O , δ): 0.82-0.88 (3H, m), 0.97 (3H, d, $J=6.6\text{Hz}$), 1.08 (3H, d, $J=5.5\text{Hz}$), 1.37 (9H, s), 1.5-4.80 (57H, complex m), 6.71-6.79 (2H, m), 7.00 (1H, br s)

MASS (m/z): 1227.4 (M^+ -Na)

Elemental Analysis Calcd. for $C_{56}H_{91}N_8O_{20}SNa \cdot 5H_2O$:

C 50.14, H 7.59, N 8.35

Found: C 49.93, H 7.51, N 8.31

Example 59

A mixture of 4-[5-[4-(6-methoxyhexyloxy)phenyl]-isoxazol-3-yl]benzoic acid (100 mg), 1-hydroxybenzotriazole (51.3 mg), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (58.2 mg) and N,N-diisopropylethylamine (66.1 μl) in N,N-dimethylformamide (2 ml) was stirred for 4.5 hours. To the reaction mixture was added starting compound

(59) (246.6 mg) and stirred for overnight. To the reaction mixture was added ethyl acetate (100 ml). The resulting precipitate was collected by filtration and washed with diisopropyl ether to give object compound (59) as a crude white powder (406.7 mg), that was used crude in the next reaction.

The following compounds [Example 60 to 62] were obtained according to a similar manner to that of Example 59.

Example 60

The object compound (60) was used directly in the next reaction without purification.

Example 61

The object compound (61) was used directly in the next reaction without purification.

Example 62

The object compound (62) was used directly in the next reaction without purification.

The following compounds [Examples 63 to 77] were obtained according to a similar manner to that of Preparation 84.

Example 63

IR (KBr): 3369.0, 1631.5, 1538.9, 1513.8, 1442.5, 1257.4 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ): 0.97 (3H, d, $J=6.7\text{Hz}$), 1.11 (3H, d, $J=5.4\text{Hz}$), 1.2-5.6 (70H, m), 6.71 (1H, d, $J=8.3\text{Hz}$), 6.77 (1H, d, $J=9.6\text{Hz}$), 6.99 (1H, s), 7.14 (2H, d, $J=8.9\text{Hz}$), 7.97 (2H, d, $J=8.6\text{Hz}$), 8.04 (2H, d, $J=8.5\text{Hz}$), 8.11 (2H, d, $J=8.3\text{Hz}$), 7.3-9.0 (6H, m)

ESI MASS (m/z): 1442.6 (M^{-1})

Elemental Analysis Calcd. for $C_{65}H_{93}N_{11}O_{22}S_2 \cdot 7H_2O$:

C 49.70, H 6.87, N 9.81

Found: C 49.43, H 6.71, N 9.71

5 Example 64

IR (KBr): 1633, 1606, 1527, 1518, 1466 cm^{-1}

NMR (DMSO- d_6 , δ): 0.96 (3H, d, $J=6.7Hz$), 1.11 (3H, d,
 $J=5.6Hz$), 1.2-2.5 (18H, m), 2.7-4.6 (34H, m), 4.6-
5.4 (8H, m), 6.7-7.2 (5H, m), 7.3-7.6 (2H, m), 7.6-
10 7.85 (4H, m), 7.95 (4H, s), 8.2-8.4 (1H, m), 8.6-
8.75 (1H, m), 8.80 (1H, s)

MASS (m/z): 1407 ($M^+ + 1$)

Example 65

15 IR (KBr): 3363.2, 1666.2, 1648.8, 1631.5, 1538.9,
1508.1, 1452.1, 1436.7, 1257.4 cm^{-1}

NMR (DMSO- d_6 , δ): 0.98 (3H, d, $J=6.8Hz$), 1.11 (3H, d,
 $J=5.7Hz$), 1.2-5.6 (53H, m), 6.71 (1H, d, $J=8.1Hz$),
6.7-6.9 (1H, m), 7.01 (1H, d, $J=1.6Hz$), 7.13 (2H,
20 d, $J=8.9Hz$), 7.45 (1H, d, $J=8.3Hz$), 7.55 (1H, s),
7.85 (2H, d, $J=8.7Hz$), 7.6-7.9 (2H, m), 7.99 (2H,
d, $J=8.8Hz$), 8.05 (2H, d, $J=8.9Hz$), 8.32 (1H, d,
 $J=7.3Hz$), 8.71 (1H, s), 8.87 (1H, d, $J=7.5Hz$)

MASS (m/z): 1266.4 ($M^- - 1$)

25 Elemental Analysis Calcd. for $C_{58}H_{77}N_9O_{21}S \cdot 8H_2O$:

C 49.32, H 6.64, N 8.92

Found: C 49.42, H 6.43, N 8.88

Example 66

30 IR (KBr): 3490, 3463, 3424, 3357, 2935, 1633, 1542,
1519 cm^{-1}

NMR (DMSO- d_6 , δ): 0.98 (3H, d, $J=6.6Hz$), 1.12 (3H, d,
 $J=5.4Hz$), 1.22-1.35 (6H, m), 1.35-2.40 (15H, m),
2.80-3.10 (3H, m), 3.18 (3H, s), 3.25 (3H, t,
35 $J=6.4Hz$), 3.45-3.60 (3H, m), 3.65-4.60 (15H, m),

4.70-5.30 (8H, m), 6.70-6.80 (2H, m), 7.00 (1H, br s), 7.40-7.75 (3H, m), 8.00-8.40 (3H, m), 8.46 (2H, d, J=8.4Hz), 8.50-9.00 (2H, m)

MASS (m/z)(API-ES-negative): 1332 (M^{+1})

5 Elemental Analysis Calcd. for $C_{58}H_{38}N_{10}O_{22}S_2 \cdot 5H_2O$:
C 49.00, H 6.19, N 9.85
Found: C 49.20, H 6.15, N 9.69

Example 67

10 IR (KBr): 3457, 3425, 3400, 3365, 2931, 1639, 1537,
1518 cm^{-1}
NMR (DMSO- d_6 , δ): 0.98 (3H, d, J=6.7Hz), 1.12 (3H, d, J=5.4Hz), 1.20-1.35 (12H, m), 1.35-1.70 (6H, m),
1.70-2.40 (7H, m), 2.80-3.10 (3H, m), 3.17 (3H, s),
15 3.26 (3H, t, J=6.4Hz), 3.30-3.50 (3H, m), 3.65-4.10
(6H, m), 4.10-4.60 (7H, m), 4.65-5.40 (8H, m),
6.60-6.80 (2H, m), 7.00 (1H, br s), 7.30-7.80 (6H, m),
8.05-8.40 (7H, m), 8.47 (2H, d, J=8.4Hz), 8.71
(1H, br s), 8.93 (1H, m)
20 MASS (m/z)(API-ES Negative): 1360 (M^{+1})
Elemental Analysis Calcd. for $C_{60}H_{82}N_{10}O_{22}S_2 \cdot 6H_2O$:
C 49.08, H 6.41, N 9.54
Found: C 48.88, H 6.41, N 9.47

25 Example 68

IR (KBr): 3457, 3424, 3400, 3367, 2935, 1637, 1509,
1261 cm^{-1}
NMR (DMSO- d_6 , δ): 0.98 (3H, d, J=6.7Hz), 1.12 (3H, d, J=5.4Hz), 1.20-1.50 (9H, m), 1.60-2.45 (9H, m),
30 3.21 (3H, s), 3.30 (2H, t, J=6.5Hz), 3.40-3.90 (6H, m), 3.90-4.55 (12H, m), 4.60-5.80 (6H, m), 6.72
(1H, d, J=8.1Hz), 6.74 (1H, dd, J=1.5 and 8.4Hz),
7.00 (1H, d, J=1.5Hz), 7.20 (2H, d, J=8.9Hz), 7.40-
7.90 (4H, m), 8.00-8.40 (6H, m), 8.94 (1H, m)
35 MASS (m/z)(API-ES-Negative): 1284 (M^{+1})

Elemental Analysis Calcd. for $C_{58}H_{78}N_{10}O_{21}S \cdot 7H_2O$:

C 49.40, H 6.53, N 9.94

Found: C 49.17, H 6.36, N 9.74

5 Example 69

IR (KBr): 3458, 3423, 3398, 3367, 2931, 1637, 1508,
1259 cm^{-1}

NMR (DMSO- d_6 , δ): 0.98 (3H, d, $J=6.7Hz$), 1.12 (3H, d,
 $J=5.5Hz$), 1.20-1.60 (12H, m), 1.65-2.45 (9H, m),
2.80-3.15 (3H, m), 3.20 (3H, s), 3.29 (3H, t,
 $J=6.5Hz$), 3.80-4.50 (17H, m), 4.60-5.30 (8H, m),
6.71 (1H, d, $J=8.2Hz$), 6.69-6.80 (1H, m), 7.00 (1H,
br s), 7.20 (2H, d, $J=8.9Hz$), 7.30-7.90 (7H, m),
8.05-8.40 (8H, m), 8.60-9.00 (2H, m)

15 MASS (m/z) (API-ES-Negative): 1312 ($M^+ + 1$)

Elemental Analysis Calcd. for $C_{60}H_{82}N_{10}O_{21}S \cdot 6H_2O$:

C 50.74, H 6.62, N 9.87

Found: C 50.48, H 6.56, N 9.60

20 Example 70

IR (KBr): 3372.9, 1664.3, 1635.3, 1361.5, 1444.4,
1257.4 cm^{-1}

NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.8Hz$), 1.12 (3H, d,
 $J=5.8Hz$), 1.2-5.3 (55H, m), 6.71 (1H, d, $J=8.1Hz$),
6.7-6.9 (1H, m), 7.00 (1H, d, $J=1.6Hz$), 7.12 (2H,
d, $J=8.9Hz$), 7.45 (1H, d, $J=8.6Hz$), 7.54 (1H, s),
7.6-7.8 (2H, m), 7.85 (2H, d, $J=8.7Hz$), 7.99 (2H,
d, $J=8.7Hz$), 8.05 (2H, d, $J=8.9Hz$), 8.25 (1H, d,
 $J=6.7Hz$), 8.81 (1H, d, $J=7.4Hz$)

25 30 MASS (m/z): 1280.4 ($M^+ - 1$)

Elemental Analysis Calcd. for $C_{59}H_{79}N_9O_{21}S \cdot 6H_2O$:

C 50.96, H 6.60, N 9.07

Found: C 50.89, H 6.43, N 8.98

Example 71

IR (KBr): 3371.0, 1631.5, 1538.9, 1506.1, 1450.2,
1436.7, 1257.4 cm^{-1}

NMR (DMSO- d_6 , δ): 0.8-1.2 (12H, m), 1.2-5.5 (58H, m),
6.71 (1H, d, $J=8.1\text{Hz}$), 6.7-6.9 (1H, m), 7.01 (1H,
d, $J=1.7\text{Hz}$), 7.12 (2H, d, $J=8.9\text{Hz}$), 7.45 (1H, d,
 $J=9.2\text{Hz}$), 7.54 (1H, s), 7.5-7.9 (2H, m), 7.85 (2H,
d, $J=8.8\text{Hz}$), 7.99 (2H, d, $J=8.8\text{Hz}$), 8.05 (2H, d,
 $J=8.9\text{Hz}$), 8.1-8.4 (1H, m), 8.70 (1H, m), 8.86 (1H,
d, $J=7.8\text{Hz}$)

MASS (m/z): 1363.5 (M^- -1)

Elemental Analysis Calcd. for $\text{C}_{64}\text{H}_{88}\text{N}_{10}\text{O}_{21}\text{S}\cdot 7\text{H}_2\text{O}$:

C 51.53, H 6.89, N 9.39

Found: C 51.23, H 6.80, N 9.27

Example 72

IR (KBr): 3363.2, 1666.2, 1648.8, 1538.9, 1506.1,
1454.1, 1436.7, 1257.4 cm^{-1}

NMR (DMSO- d_6 , δ): 0.8-1.2 (12H, m), 1.2-5.3 (60H, m),
6.71 (1H, d, $J=8.2\text{Hz}$), 6.7-6.9 (1H, m), 7.01 (1H,
s), 7.12 (2H, d, $J=8.9\text{Hz}$), 7.54 (1H, s), 7.3-7.8
(3H, m), 7.85 (2H, d, $J=8.7\text{Hz}$), 7.9-8.2 (4H, m),
8.2-8.4 (1H, m), 8.7 (1H, s), 8.8-9.0 (1H, m)

MASS (m/z): 1377.6 (M^- -1)

Elemental Analysis Calcd. for $\text{C}_{65}\text{H}_{90}\text{N}_{10}\text{O}_{21}\text{S}\cdot 8\text{H}_2\text{O}$:

C 51.24, H 7.01, N 9.19

Found: C 51.52, H 7.06, N 9.16

Example 73

IR (KBr): 3363.2, 1631.5, 1538.9, 1510.0, 1438.6,
1243.9 cm^{-1}

NMR (DMSO- d_6 , δ): 0.98 (3H, d, $J=6.7\text{Hz}$), 1.11 (3H, d,
 $J=5.7\text{Hz}$), 1.18 (6H, d, $J=6.0\text{Hz}$), 1.2-5.5 (44H, m),
6.71 (1H, d, $J=8.2\text{Hz}$), 6.78 (1H, d, $J=9.8\text{Hz}$), 7.00
(1H, s), 7.11 (2H, d, $J=8.9\text{Hz}$), 7.46 (1H, s), 7.3-

7.8 (3H, m), 7.76 (2H, d, $J=8.7\text{Hz}$), 7.99 (2H, d, $J=8.6\text{Hz}$), 8.05 (2H, d, $J=8.7\text{Hz}$), 8.2-9.0 (3H, m)
MASS (m/z): 1249.4 (M^{-1})

5 Example 74

MASS (m/z): 1377.4 (M^{+1})

Example 75

MASS (m/z): 1405.4 (M^{+1})

10

Example 76

NMR (DMSO- d_6 , δ): 0.86 (3H, d, $J=6.3\text{Hz}$), 0.98 (3H, d, $J=6.8\text{Hz}$), 1.11 (3H, d, $J=5.8\text{Hz}$), 1.20-5.23 (56H, m), 6.69-8.93 (17H, m)

15

MASS (m/z): 1333.4 (M^{+1})

Example 77

MASS (m/z): 1297.3 (M^{+1})

20 Example 78

A mixture of starting compound (78) (100 mg), N-tert-butoxycarbonyl- β -alanine (13.5 mg), 1-hydroxybenzotriazole (15.5 mg), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (29.4 mg) and N,N-diisopropylethylamine (28.2 μl) in N,N-dimethylformamide (1 ml) was stirred for 3 hours at 30°C. To the reaction mixture was added ethyl acetate (30 ml). The resulting precipitate was collected by filtration and washed with diisopropyl ether to give a crude white powder (137.3 mg). The crude powder was purified by column chromatography on ODS (YMC-gel ODS-AM-S-50 (Trademark: prepared by YMC Co., Ltd.)) (30% acetonitrile aqueous solution). The fractions containing the object compound were combined, and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give object compound (78).

35

IR (KBr): 3372.9, 1658.5, 1635.3, 1546.8, 1529.3,
1517.7, 1444.4, 1255.4 cm^{-1}

MASS (m/z): 1468.3 ($\text{M}^{\text{--Na}}$)

Elemental Analysis Calcd. for $\text{C}_{66}\text{H}_{90}\text{N}_{11}\text{NaO}_{23}\text{S}_2 \cdot 6\text{H}_2\text{O}$:

C 49.52, H 6.42, N 9.63

Found: C 49.34, H 6.33, N 9.73

The following compounds [Examples 79 to 86] were
obtained according to a similar manner to that of Example 78.

Example 79

IR (KBr): 3374.8, 1658.5, 1635.3, 1529.3, 1517.7,
1444.4, 1257.4 cm^{-1}

MASS (m/z): 1368.3 ($\text{M}^{\text{--Na}}$)

Example 80

IR (KBr): 3372.9, 1656.6, 1635.3, 1531.2, 1517.7,
1444.4, 1255.4 cm^{-1}

MASS (m/z): 1496.4 ($\text{M}^{\text{--Na}}$)

Elemental Analysis Calcd. for $\text{C}_{68}\text{H}_{94}\text{N}_{11}\text{NaO}_{23}\text{S}_2 \cdot 6\text{H}_2\text{O}$:

C 50.15, H 6.56, N 9.46

Found: C 49.90, H 6.36, N 9.34

Example 81

IR (KBr): 3392.2, 1664.3, 1635.3, 1446.4, 1255.4 cm^{-1}

MASS (m/z): 1611.5 ($\text{M}^{\text{--Na}}$)

Elemental Analysis Calcd. for $\text{C}_{73}\text{H}_{103}\text{N}_{12}\text{NaO}_{25}\text{S}_2 \cdot 7\text{H}_2\text{O}$:

C 49.76, H 6.69, N 9.54

Found: C 49.73, H 6.59, N 9.46

Example 82

IR (KBr): 3372.9, 1658.5, 1635.3, 1546.6, 1531.2,
1517.7, 1444.4, 1255.4 cm^{-1}

MASS (m/z): 1498.5 ($\text{M}^{\text{--Na}}$)

Elemental Analysis Calcd. for $\text{C}_{67}\text{H}_{92}\text{N}_{11}\text{NaO}_{24}\text{S}_2 \cdot 8\text{H}_2\text{O}$:

C 48.28, H 6.53, N 9.24

Found: C 48.50, H 6.35, N 9.21

Example 83

5 IR (KBr): 3378.7, 1658.5, 1635.3, 1546.6, 1529.3,
1517.7, 1446.4, 1255.4 cm^{-1}

MASS (m/z): 1625.5 ($\text{M}^{\text{--Na}}$)

Elemental Analysis Calcd. for $\text{C}_{74}\text{H}_{105}\text{N}_{12}\text{NaO}_{25}\text{S}_2\cdot 8\text{H}_2\text{O}$:

C 49.55, H 6.80, N 9.37

10 Found: C 49.70, H 6.68, N 9.38

Example 84

IR (KBr): 3367.7, 1658.5, 1635.3, 1546.6, 1529.3,
1517.7, 1444.4, 1255.4 cm^{-1}

15 MASS (m/z): 1634.6 ($\text{M}^{\text{--Na}}$)

Elemental Analysis Calcd. for $\text{C}_{74}\text{H}_{100}\text{N}_{13}\text{NaO}_{25}\text{S}_2\cdot 7\text{H}_2\text{O}$:

C 49.80, H 6.44, N 10.20

Found: C 49.71, H 6.34, N 10.29

20 Example 85

IR (KBr): 3355.5, 1658.5, 1635.3, 1546.6, 1531.2,
1517.7, 1446.4, 1257.4 cm^{-1}

MASS (m/z): 1693.5 ($\text{M}^{\text{--Na}}$)

Elemental Analysis Calcd. for $\text{C}_{80}\text{H}_{101}\text{N}_{12}\text{NaO}_{25}\text{S}_2\cdot 7\text{H}_2\text{O}$:

25 C 52.11, H 6.29, N 9.12

Found: C 51.96, H 6.28, N 9.06

Example 86

30 IR (KBr): 3372.9, 1658.5, 1635.3, 1546.6, 1531.2,
1517.7, 1446.4, 1257.4 cm^{-1}

MASS (m/z): 1645.4 ($\text{M}^{\text{--Na}}$)

Elemental Analysis Calcd. for $\text{C}_{76}\text{H}_{101}\text{N}_{12}\text{NaO}_{25}\text{S}_2\cdot 8\text{H}_2\text{O}$:

C 52.32, H 6.50, N 9.27

Found: C 50.56, H 6.37, N 9.29

35

The following compounds [Examples 87 to 95] were obtained according to a similar manner to that of Preparation 10.

5 Example 87

IR (KBr): 2935, 1651, 1541, 1514, 1454, 1514, 1257 cm^{-1}

NMR ($\text{DMSO-d}_6 + \text{D}_2\text{O}$, δ): 0.97 (3H, d, $J=6.7\text{Hz}$), 1.12 (3H, br s), 1.20-5.00 (44H, m), 3.21 (3H, s), 3.31 (2H, t, $J=6.4\text{Hz}$), 4.07 (2H, t, $J=6.2\text{Hz}$), 6.70-6.80 (2H, m), 7.00 (1H, s), 7.14 (2H, d, $J=8.9\text{Hz}$), 7.98 (2H, d, $J=8.9\text{Hz}$), 8.09 (4H, br s)

MASS (m/z): 1443.3 ($\text{M}^+ + \text{Na}$)

Elemental Analysis Calcd. for $\text{C}_{62}\text{H}_{81}\text{N}_{10}\text{O}_{23}\text{S}_2\text{Na}\cdot 7\text{H}_2\text{O}$:

C 48.12, H 6.19, N 9.05

Found: C 47.94, H 6.07, N 8.99

Example 88

MASS (m/z): 1492 (M^+)

20 Example 89

IR (KBr): 3490, 3463, 3455, 3423, 3363, 2937, 1631, 1544 cm^{-1}

NMR (DMSO-d_6 , δ): 0.97 (3H, d, $J=6.6\text{Hz}$), 1.21 (3H, d, $J=5.4\text{Hz}$), 1.20-1.40 (9H, m), 1.40-2.40 (12H, m), 2.90-3.20 (3H, m), 3.21 (3H, s), 3.33 (3H, t, $J=6.4\text{Hz}$), 3.65-4.30 (9H, m), 4.40-5.00 (6H, m), 5.11-5.30 (6H, m), 5.80-6.10 (1H, m), 6.69-6.80 (2H, m), 6.96 (1H, br s), 7.13 (1H, br s), 7.40-7.90 (3H, m), 8.00-8.30 (7H, m), 8.47 (2H, d, $J=8.3\text{Hz}$), 8.72 (1H, br s), 8.75-8.90 (1H, m)

MASS (m/z)(API-ES-Negative): 1415 ($\text{M}^+ - 1 - \text{Na}$)

Elemental Analysis Calcd. for $\text{C}_{62}\text{H}_{81}\text{N}_{10}\text{NaO}_{24}\text{S}_2\cdot 2.5\text{H}_2\text{O}$:

C 50.20, H 5.80, N 9.45

Found: C 50.05, H 5.80, N 9.29

Example 90

IR (KBr): 3369, 1639, 1542, 1519, 1272 cm^{-1}

5 NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.7\text{Hz}$), 1.14 (3H, d, $J=5.8\text{Hz}$), 1.20–1.35 (12H, m), 1.35–1.70 (6H, m), 1.70–2.40 (6H, m), 3.17 (3H, s), 3.25 (3H, t, $J=6.3\text{Hz}$), 3.30–3.50 (2H, m), 3.60–4.30 (9H, m), 4.40–4.90 (6H, m), 5.10–5.30 (6H, m), 5.80–5.90 (1H, m), 6.71 (1H, d, $J=8.2\text{Hz}$), 6.60–6.80 (1H, m),
10 6.96 (1H, br s), 7.00–7.20 (1H, m), 7.40–7.90 (3H, m), 8.00–8.20 (6H, m), 8.48 (2H, d, $J=8.4\text{Hz}$), 8.72 (1H, br s), 8.70–8.8 (1H, m)

MASS (m/z): 1441 ($M^+ - 1 - \text{Na}$)

Elemental Analysis Calcd. for $\text{C}_{64}\text{H}_{85}\text{N}_{10}\text{NaO}_{24}\text{S}_2 \cdot 6\text{H}_2\text{O}$:

15 C 48.82, H 6.17, N 8.90
Found: C 48.83, H 6.24, N 8.78

Example 91

IR (KBr): 3363, 2935, 1637, 1626, 1540, 1261 cm^{-1}

20 NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.8\text{Hz}$), 1.13 (3H, d, $J=5.8\text{Hz}$), 1.30–1.60 (12H, m), 1.70–2.50 (7H, m), 2.80–3.25 (3H, m), 3.21 (3H, s), 3.30 (2H, t, $J=6.5\text{Hz}$), 3.65–4.30 (12H, m), 4.40–5.00 (9H, m), 5.10–5.40 (7H, m), 5.80–6.05 (1H, m), 6.71 (1H, d, $J=8.1\text{Hz}$), 6.75 (1H, dd, $J=8.3$ and 1.6Hz), 6.96 (1H, d, $J=1.6\text{Hz}$), 7.10 (1H, br s), 7.20 (1H, d, $J=8.8\text{Hz}$), 7.40–7.80 (3H, m), 8.00–8.20 (7H, m),
25 8.72 (1H, br s), 8.70–8.80 (1H, m)

MASS (m/z) (API-ES-Negative): 1367 ($M^+ + 1 - \text{Na}$)

30 Elemental Analysis Calcd. for $\text{C}_{62}\text{H}_{81}\text{N}_{10}\text{NaO}_{23}\text{S}_2 \cdot 6\text{H}_2\text{O}$:
C 69.70, H 6.21, N 9.35
Found: C 49.86, H 6.22, N 9.35

Example 92

35 IR (KBr): 3363, 2933, 2859, 1637, 1540, 1510, 1444,

1261 cm^{-1}

5 NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.7\text{Hz}$), 1.13 (3H, d, $J=5.8\text{Hz}$), 1.28-1.60 (15H, m), 1.69-2.45 (8H, m),
2.80-3.30 (3H, m), 3.20 (3H, s), 3.26 (2H, t, $J=6.4\text{Hz}$), 3.60-4.30 (12H, m), 4.40-5.00 (9H, m),
5.10-5.30 (7H, m), 5.75-6.05 (1H, m), 6.68 (1H, d, $J=8.1\text{Hz}$), 6.75 (1H, dd, $J=1.7$ and 8.3Hz), 6.96 (1H, d, $J=1.7\text{Hz}$), 7.10-7.20 (1H, m), 7.15 (2H, d, $J=8.9\text{Hz}$), 7.40-7.90 (3H, m), 8.00-8.20 (7H, m),
10 8.60-8.80 (2H, m)

MASS (m/z) (APCI-ES-Negative): 1395 ($M^+ + 1 - \text{Na}$)

Elemental Analysis Calcd. for $\text{C}_{64}\text{H}_{85}\text{N}_{10}\text{NaO}_{23}\text{S}_6\text{H}_2\text{O}$:

C 50.36, H 6.36, N 9.18

Found: C 50.22, H 6.31, N 9.10

15

Example 93

MASS (m/z): 1461.4 ($M^+ - 1$)

Example 94

20 MASS (m/z): 1489.5 ($M^+ - 1$)

Example 95

NMR (DMSO- d_6 , δ): 0.87 (3H, d, $J=6.3\text{Hz}$), 0.97 (3H, d, $J=6.7\text{Hz}$), 1.14-5.29 (81H, m), 6.69-8.72 (18H, m)

25 MASS (m/z): 1418.4 (free)

The following compounds [Examples 96 to 117] were obtained according to a similar manner to that of Example 19.

30 Example 96

IR (KBr): 1632, 1539, 1520, 1443 cm^{-1}

NMR (DMSO- d_6 + D_2O , δ): 0.97 (3H, d, $J=6.64\text{Hz}$), 1.07 (3H, d, $J=5.68\text{Hz}$), 1.15-1.70 (3H, m), 1.70-2.50 (5H, m), 2.70-3.40 (5H, m), 4.10-4.60 (8H, m),
35 4.70-4.85 (2H, m), 5.00-5.35 (2H, m), 5.70-6.10

(1H, m), 6.50-6.80 (2H, m), 6.99 (1H, s)

ESI MASS (m/z)(Positive): 1019.3 ($M^+ + Na$)

Elemental Analysis Calcd. for $C_{39}H_{57}N_8O_{19}SNa \cdot 8H_2O$:

C 41.05, H 6.45, N 9.82

5

Found: C 41.02, H 6.19, N 9.73

Example 97

IR (KBr): 1647, 1635, 1539, 1518, 1439, 1269 cm^{-1}

10 NMR (DMSO- d_6 + D_2O , δ): 0.95 (3H, d, $J=6.66Hz$), 1.12
(3H, d, $J=5.76Hz$), 1.20-1.60 (4H, m), 1.70-2.45
(4H, m), 2.65-3.35 (6H, m), 3.70-4.55 (16H, m),
4.60-4.80 (2H, m), 5.10-5.40 (2H, m), 5.70-6.00
(1H, m), 6.75 (1H, d, $J=8.15Hz$), 6.83 (1H, d,
 $J=10.1Hz$), 7.09 (1H, s)

15 ESI MASS (m/z)(Negative): 989.3 (M^+)

Elemental Analysis Calcd. for $C_{39}H_{58}N_8O_{20}SNa \cdot 5H_2O$:

C 43.33, H 6.34, N 10.37

Found: C 43.17, H 6.25, N 10.30

20 Example 98

IR (KBr): 1680, 1662, 1639, 1539, 1514, 1439 cm^{-1}

NMR (DMSO- d_6 + D_2O , δ): 0.98 (3H, d, $J=6.77Hz$), 1.09
(3H, d, $J=6.01Hz$), 1.15-1.40 (1H, m), 1.45-2.00
(4H, m), 2.10-2.50 (4H, m), 2.70-2.90 (3H, m),
25 3.15-3.40 (4H, m), 3.70-4.00 (6H, m), 4.10-4.50
(6H, m), 4.75-4.80 (2H, m), 6.70-6.80 (2H, m), 7.03
(1H, s)

ESI MASS (m/z)(Positive): 892.2 ($M^+ + 1$)

Elemental Analysis Calcd. for $C_{35}H_{54}N_8O_{17}S \cdot 4H_2O$:

30 C 43.65, H 6.49, N 11.64

Found: C 43.51, H 6.40, N 11.48

Example 99

NMR (DMSO- d_6 + D_2O , δ): 0.96 (3H, d, $J=6.69Hz$), 1.09

(3H, d, J=5.05Hz), 1.15-2.40 (8H, m), 2.65-3.30
(3H, m), 3.70-4.90 (18H, m), 6.65-6.85 (2H, m),
6.99 (1H, s)

ESI MASS (m/z)(Positive): 1013.4 (M^+ +Na)

5

Example 100

IR (KBr): 3377, 2935, 1658.5, 1641, 1531, 1518, 1444,
1284, 1257, 1113, 1088, 1043 cm^{-1}

10

NMR (DMSO- d_6 , δ): 0.96 (3H, d, J=6.7Hz), 1.05 (3H, d,
J=5.6Hz), 3.21 (3H, s), 4.07 (2H, t, J=6.5Hz), 1.2-
5.2 (57H, complex m), 6.70 (1H, d, J=8.1Hz), 6.78-
6.83 (1H, m), 6.99 (1H, br s), 7.13 (2H, d,
J=8.8Hz), 7.4-7.6 (2H, m), 7.7-7.9 (1H, m), 7.97
(2H, d, J=8.8Hz), 8.09 (4H, s), 8.50-8.60 (1H, m),
8.71 (1H, s), 8.68-8.80 (1H, m)

15

MASS (m/z): 1407.3 (M^+)

Elemental Analysis Calcd. for $\text{C}_{64}\text{H}_{85}\text{N}_{11}\text{O}_{21}\text{S}_2 \cdot 7\text{H}_2\text{O}$:

C 50.09, H 6.50, N 10.04

Found: C 50.01, H 6.41, N 9.91

20

Example 101

NMR (DMSO- d_6 , δ): 0.96 (3H, d, J=6.8Hz), 1.1-5.6 (72H,
m), 6.6-6.9 (2H, m), 6.99 (1H, s), 7.14 (2H, d,
J=8.9Hz), 7.97 (2H, d, J=8.7Hz), 8.08 (4H, s), 7.4-
9.0 (6H, m)

25

MASS (m/z): 1411.3 (M^{-1})

Example 102

IR (KBr): 3384.5, 1658.5, 1635.3, 1444.4, 1257.4 cm^{-1}

30

NMR (DMSO- d_6 , δ): 0.96 (3H, d, J=6.7Hz), 1.14 (3H, d,
J=5.3Hz), 1.3-5.4 (62H, m), 6.70 (1H, d, J=8.2Hz),
6.77 (1H, d, J=9.8Hz), 6.96 (1H, s), 7.13 (2H, d,
J=8.9Hz), 7.97 (2H, d, J=8.8Hz), 8.05 (2H, d,
J=8.8Hz), 8.11 (2H, d, J=8.9Hz), 7.4-9.0 (6H, m)

MASS (m/z): 1354.3 (M^{-1})

Example 103

5 IR (KBr): 3401.8, 1664.3, 1635.3, 1627.6, 1446.4,
1257.4 cm^{-1}
NMR (DMSO- d_6 , δ): 0.96 (3H, d, $J=6.8\text{Hz}$), 1.0-5.6 (69H,
m), 6.68 (1H, d, $J=8.1\text{Hz}$), 6.78 (1H, d, $J=8.7\text{Hz}$),
6.93 (1H, d, $J=8.4\text{Hz}$), 7.13 (2H, d, $J=8.8\text{Hz}$), 7.97
(2H, d, $J=8.8\text{Hz}$), 8.08 (4H, s), 7.4-9.0 (6H, m)
10 MASS (m/z): 1382.4 (M^{-1})

Example 104

IR (KBr): 3403.7, 1664.3, 1635.3, 1446.4, 1257.4 cm^{-1}
NMR (DMSO- d_6 , δ): 0.96 (3H, d, $J=6.6\text{Hz}$), 1.0-5.5 (71H,
15 m), 7.13 (2H, d, $J=8.9\text{Hz}$), 7.97 (2H, d, $J=8.8\text{Hz}$),
6.6-8.9 (13H, m)
MASS (m/z): 1420.2 ($M^{+}+\text{Na}$)

Example 105

20 IR (KBr): 3367.1, 1635.3, 1531.2, 1517.7, 1444.4,
1257.4 cm^{-1}
NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.8\text{Hz}$), 1.12 (3H, d,
 $J=5.9\text{Hz}$), 1.2-5.4 (64H, m), 6.70 (1H, d, $J=8.1\text{Hz}$),
6.77 (1H, d, $J=10.0\text{Hz}$), 6.99 (1H, s), 7.14 (2H, d,
25 $J=8.9\text{Hz}$), 7.44 (1H, d, $J=8.6\text{Hz}$), 7.62 (1H, m), 7.78
(1H, m), 7.97 (2H, d, $J=8.8\text{Hz}$), 8.05 (2H, d,
 $J=8.8\text{Hz}$), 8.11 (2H, d, $J=8.7\text{Hz}$), 8.1-8.3 (1H, m),
8.6-8.9 (2H, m)
MASS (m/z): 1368.5 (M^{-1})
30 Elemental Analysis Calcd. for $\text{C}_{62}\text{H}_{87}\text{N}_{11}\text{O}_{20}\text{S}_2\cdot 8\text{H}_2\text{O}$:
C 49.16, H 6.85, N 10.17
Found: C 49.29, H 6.50, N 10.08

Example 106

IR (KBr): 2935.1, 2865.7, 1648.8, 1538.9, 1513.8,
1452.1, 1440.6, 1257.4 cm^{-1}

5 NMR (DMSO- d_6 + D_2O , δ): 0.97 (3H, d, $J=6.3\text{Hz}$), 1.11 (3H,
d, $J=5.7\text{Hz}$), 1.2-4.9 (55H, complex m), 3.21 (3H,
s), 3.31 (2H, t, $J=6.5\text{Hz}$), 6.7-6.81 (2H, m), 7.03
(1H, br s), 7.14 (2H, d, $J=8.9\text{Hz}$), 7.98 (2H, d,
 $J=8.9\text{Hz}$), 8.0-8.15 (4H, m)

MASS (m/z): 1463.4 (M^+-1)

10 Elemental Analysis Calcd. for $C_{67}H_{92}N_{12}O_{21}S_2 \cdot 7H_2O$:

C 50.56, H 6.71, N 10.56

Found: C 50.34, H 6.38, N 10.46

Example 107

15 IR (KBr): 2933, 2860, 1657, 1635, 1529, 1516, 1444,
1387, 1257, 1178, 1115, 1088, 1043 cm^{-1}

NMR (DMSO- d_6 + D_2O , δ): 0.97 (3H, d, $J=6.7\text{Hz}$), 1.12 (3H,
d, $J=5.9\text{Hz}$), 1.4-4.85 (50H, complex m), 3.21 (3H,
s), 3.31 (2H, t, $J=6.3\text{Hz}$), 6.7-6.8 (2H, m), 7.02
20 (1H, br s), 7.14 (2H, d, $J=8.9\text{Hz}$), 7.97 (2H, d,
 $J=8.9\text{Hz}$), 8.02-8.14 (4H, m)

MASS (m/z): 1381.4 (M^+-1)

Elemental Analysis Calcd. for $C_{63}H_{87}N_{11}O_{20}S_2 \cdot 6H_2O$:

C 50.76, H 6.69, N 10.34

25 Found: C 50.43, H 6.70, N 10.20

Example 108

IR (KBr): 2935, 2866, 1660, 1631.5, 1525, 1442.5, 1412,
1257, 1178, 1111, 1088, 1043 cm^{-1}

30 NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.7\text{Hz}$), 1.10 (3H, d,
 $J=5.5\text{Hz}$), 1.2-4.9 (55H, complex m), 3.21 (3H, s),
3.31 (2H, t, $J=6.4\text{Hz}$), 6.75 (2H, br), 7.05 (1H,
br), 7.14 (2H, d, $J=8.8\text{Hz}$), 7.99 (2H, d, $J=8.8\text{Hz}$),
8.01-8.16 (4H, m)

MASS (m/z): 1510.5 (M^+-1)

Elemental Analysis Calcd. for $C_{68}H_{94}N_{12}O_{23}S_2 \cdot 7H_2O$:

C 49.87, H 6.65, N 10.26

Found: C 49.64, H 6.57, N 10.15

5

Example 109

IR (KBr): 3372.9, 1658.5, 1635.3, 1529.3, 1517.7,
1446.4, 1255.4 cm^{-1}

10 NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.7Hz$), 1.15 (3H, d,
 $J=5.1Hz$), 1.2-5.6 (58H, m), 6.71 (1H, d, $J=8.1Hz$),
6.77 (1H, d, $J=10.0Hz$), 6.97 (1H, s), 7.13 (2H, d,
 $J=8.9Hz$), 7.97 (2H, d, $J=8.8Hz$), 8.09 (4H, s), 7.3-
9.0 (7H, m)

MASS (m/z): 1510.5 (M^--Na)

15 Elemental Analysis Calcd. for $C_{61}H_{82}N_{11}NaO_{21}S_2 \cdot 8H_2O$:

C 47.68, H 6.43, N 10.03

Found: C 49.75, H 6.19, N 10.23

Example 110

20 IR (KBr): 3374.8, 1658.5, 1635.3, 1529.3, 1517.7,
1444.4, 1257.4 cm^{-1}

25 NMR (DMSO- d_6 , δ): 0.98 (3H, d, $J=6.8Hz$), 1.13 (3H, d,
 $J=5.6Hz$), 1.2-5.4 (64H, m), 6.71 (1H, d, $J=8.1Hz$),
6.78 (1H, d, $J=10.0Hz$), 7.03 (1H, s), 7.13 (2H, d,
 $J=8.9Hz$), 7.97 (2H, d, $J=8.7Hz$), 8.0-8.2 (4H, m),
7.3-9.0 (7H, m)

MASS (m/z): 1410.54 (M^--Na)

Elemental Analysis Calcd. for $C_{64}H_{88}N_{11}NaO_{21}S_2 \cdot 6H_2O$:

C 49.83, H 6.53, N 9.99

30 Found: C 49.72, H 6.40, N 9.99

Example 111

IR (KBr): 3374.8, 1658.5, 1635.3, 1546.6, 1531.2,
1517.7, 1444.4, 1257.4 cm^{-1}

5 NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.7\text{Hz}$), 1.14 (3H, d,
 $J=5.4\text{Hz}$), 1.2-5.6 (62H, m), 6.71 (1H, d, $J=8.2\text{Hz}$),
6.78 (1H, d, $J=9.8\text{Hz}$), 7.02 (1H, s), 7.13 (2H, d,
 $J=8.9\text{Hz}$), 7.97 (2H, d, $J=8.8\text{Hz}$), 8.06 (2H, d,
 $J=9.1\text{Hz}$), 8.11 (2H, d, $J=8.8\text{Hz}$), 7.3-9.0 (7H, m)

MASS (m/z): 1396.4 (M^- -Na)

10 Elemental Analysis Calcd. for $\text{C}_{63}\text{H}_{86}\text{N}_{11}\text{NaO}_{21}\text{S}_2 \cdot 7\text{H}_2\text{O}$:

C 48.92, H 6.52, N 9.96

Found: C 48.92, H 6.32, N 9.85

Example 112

15 IR (KBr): 3359.4, 1658.5, 1635.3, 1546.6, 1531.2,
1517.7, 1444.4, 1257.4 cm^{-1}

NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.6\text{Hz}$), 1.16 (3H, d,
 $J=5.8\text{Hz}$), 1.2-5.8 (64H, m), 6.71 (1H, d, $J=8.1\text{Hz}$),
6.77 (1H, d, $J=9.7\text{Hz}$), 6.98 (1H, s), 7.13 (2H, d,
20 $J=8.9\text{Hz}$), 7.97 (2H, d, $J=8.7\text{Hz}$), 8.08 (4H, s), 7.3-
9.0 (7H, m)

MASS (m/z): 1411.4 (M^- -Na)

Elemental Analysis Calcd. for $\text{C}_{63}\text{H}_{85}\text{N}_{12}\text{NaO}_{21}\text{S}_2 \cdot 7\text{H}_2\text{O}$:

C 48.45, H 6.52, N 10.76

25 Found: C 48.44, H 6.32, N 10.62

Example 113

IR (KBr): 3374.8, 1658.5, 1635.3, 1546.6, 1531.2,
1517.7, 1444.4, 1257.4 cm^{-1}

30 NMR (DMSO- d_6 , δ): 0.96 (3H, d, $J=6.5\text{Hz}$), 1.11 (3H, d,
 $J=4.5\text{Hz}$), 1.2-5.8 (60H, m), 6.68 (1H, d, $J=8.0\text{Hz}$),
6.80 (1H, d, $J=7.9\text{Hz}$), 6.93 (1H, d, $J=9.5\text{Hz}$), 7.13
(2H, d, $J=8.8\text{Hz}$), 7.97 (2H, d, $J=8.7\text{Hz}$), 8.08 (4H,
s), 7.3-9.0 (7H, m)

MASS (m/z): 1398.4 (M^- -Na)

Example 114

IR (KBr): 3374.8, 1658.5, 1635.3, 1546.6, 1531.2,
5 1517.7, 1444.4, 1257.4 cm^{-1}
NMR ($\text{DMSO}-d_6$, δ): 0.97 (3H, d, $J=6.5\text{Hz}$), 1.15 (3H, d,
 $J=5.8\text{Hz}$), 1.2-5.6 (65H, m), 6.70 (1H, d, $J=8.2\text{Hz}$),
6.77 (1H, d, $J=9.8\text{Hz}$), 6.97 (1H, s), 7.13 (2H, d,
 $J=8.8\text{Hz}$), 7.97 (2H, d, $J=8.7\text{Hz}$), 8.08 (4H, s), 7.3-
10 9.0 (7H, m)

MASS (m/z): 1398.4 (M^- -Na)

Elemental Analysis Calcd. for $\text{C}_{64}\text{H}_{89}\text{N}_{12}\text{NaO}_{21}\text{S}_2\cdot 9\text{H}_2\text{O}$:

C 47.69, H 6.69, N 10.43

Found: C 47.78, H 6.32, N 10.17

15

Example 115

MASS (m/z): 1434.4 (M^- -Na)

Example 116

IR (KBr): 3348, 1658.5, 1633 cm^{-1}
20 NMR ($\text{DMSO}-d_6 + \text{D}_2\text{O}$, δ): 0.82-0.89 (3H, m), 0.95-1.03
(6H, m), 1.1-4.78 (57H, complex m), 6.7-6.8 (2H,
m), 7.03 (1H, br s)

MASS (m/z): 1128.5 (M^+-1)

25 Elemental Analysis Calcd. for $\text{C}_{51}\text{H}_{84}\text{N}_8\text{O}_{18}\text{S}\cdot 5\text{H}_2\text{O}$:

C 50.23, H 7.77, N 9.19

Found: C 50.10, H 7.78, N 9.09

Example 117

30 NMR ($\text{DMSO}-d_6$, δ): 0.98 (3H, d, $J=6.6\text{Hz}$), 1.10 (3H, d,
 $J=5.4\text{Hz}$), 0.74-2.69 (22H, m), 2.80-3.05 (3H, m),
3.15-4.62 (18H, m), 4.68-5.35 (8H, m), 6.71 (1H, d,
 $J=8.1\text{Hz}$), 6.78 (1H, d, $J=8.1\text{Hz}$), 7.01 (1H, s), 7.12
(2H, d, $J=8.6\text{Hz}$), 7.37-8.10 (3H, m), 7.73 (4H, d,
35 $J=8.5\text{Hz}$), 7.97 (2H, d, $J=8.3\text{Hz}$), 8.22-8.40 (1H, m),

8.65-8.88 (2H, m)

MASS (m/z): 1224.4 ($M^{+}-1$)

Example 118

- 5 To a solution of a mixture of starting compound (118) (440 mg), 1-1-dimethyl-4-oxo-piperidinium Iodide(122 mg) and acetic acid (55 μ l) in a mixture of methanol (6 ml) and DMF (3 ml) was added sodium cyanoborohydride (30 mg) with stirring at ambient temperature, and the mixture was stirred
- 10 at the same temperature overnight. To the reaction mixture was added ethyl acetate and the resulting precipitates were collected by filtration and dried in vacuo. The precipitates were dissolved in a mixture of pH 6.86 standard buffer solution and acetonitrile, and the solution was subjected to
- 15 column chromatography on ODS (Daiso-gel, SP-120-40/60-ODS-B (Trademark: prepared by Daiso Co., Ltd.)) eluting with 30% acetonitrile in water. The fractions containing the object compound were collected and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give
- 20 object compound (118) (350 mg).

IR (KBr): 3353, 2942, 1673, 1633, 1517, 1463, 1438, 1268, 1232, 1201, 1135, 1085, 1045 cm^{-1}

- NMR (DMSO- d_6 , δ): 0.98 (3H, d, $J=6.7\text{Hz}$), 1.10 (3H, d, $J=5.7\text{Hz}$), 1.3-1.6 (6H, m), 1.6-2.7 (17H, m), 2.7-4.2 (37H, m), 4.2-4.6 (7H, m), 4.80 (2H, d, $J=6.7\text{Hz}$), 5.2 (1H, m), 5.4 (1H, m), 6.77 (2H, m), 7.05 (1H, s), 7.08 (2H, d, $J=8.3\text{Hz}$), 7.45 (1H, d, $J=8.8\text{Hz}$), 7.56 (1H, d, $J=7.5\text{Hz}$), 7.75 (2H, d, $J=8.8\text{Hz}$), 7.90 (1H, m), 7.96 (4H, s), 8.40 (1H, d, $J=7.2\text{Hz}$), 8.6 (1H, m), 8.70 (1H, d, $J=6.9\text{Hz}$), 8.79 (1H, s)
- 25
- 30

MASS (m/z): 1513.3 ($M^{+}+\text{Na}$)

- The following compounds [Examples 119 to 137] were
- 35 obtained according to a similar manner to that of Example

118.Example 119

IR (KBr): 3353, 2937, 1673, 1635, 1529, 1517, 1463,
1436, 1230, 1199, 1133, 1085, 1045 cm^{-1}

NMR (DMSO-d_6 , δ): 0.98 (3H, d, $J=6.7\text{Hz}$), 1.10 (3H, d, $J=5.7\text{Hz}$), 1.30 (4H, m), 1.50 (6H, m), 1.6-2.7 (17H, m), 2.7-4.2 (37H, m), 4.2-4.6 (7H, m), 4.80 (2H, d, $J=6.7\text{Hz}$), 5.14 (1H, m), 5.35 (1H, m), 6.72 (1H, d, $J=8.8\text{Hz}$), 6.80 (1H, d, $J=8.8\text{Hz}$), 7.05 (1H, s), 7.08 (2H, d, $J=8.8\text{Hz}$), 7.45 (1H, d, $J=8.8\text{Hz}$), 7.56 (1H, d, $J=7.5\text{Hz}$), 7.75 (2H, d, $J=8.8\text{Hz}$), 7.91 (1H, m), 7.96 (4H, s), 8.40 (1H, d, $J=7.2\text{Hz}$), 8.6 (1H, m), 8.70 (1H, d, $J=6.9\text{Hz}$), 8.80 (1H, s)

MASS (m/z): 1541.6 ($\text{M}^+ + \text{Na}$)

Elemental Analysis Calcd. for $\text{C}_{71}\text{H}_{99}\text{N}_{13}\text{O}_{20}\text{S}_2 \cdot 2\text{TFA} \cdot 9\text{H}_2\text{O}$:

C 47.19, H 6.28, N 9.54

Found: C 47.13, H 6.01, N 9.47

20 Example 120

IR (KBr): 3355, 2937, 1673, 1635, 1529, 1519, 1444,
1276, 1253, 1201, 1135, 1085, 1045 cm^{-1}

NMR (DMSO-d_6 , δ): 0.95 (3H, d, $J=6.7\text{Hz}$), 0.98 (3H, d, $J=6.7\text{Hz}$), 1.10 (3H, d, $J=5.7\text{Hz}$), 1.56 (5H, m), 1.6-2.7 (17H, m), 2.8-3.8 (26H, m), 3.8-4.2 (9H, m), 4.2-4.6 (7H, m), 4.8 (3H, m), 5.17 (1H, m), 5.4 (1H, m), 6.71 (1H, d, $J=8.2\text{Hz}$), 6.80 (1H, d, $J=8.2\text{Hz}$), 7.05 (1H, s), 7.20 (2H, d, $J=8.8\text{Hz}$), 7.44 (1H, d, $J=7.8\text{Hz}$), 7.62 (1H, d, $J=7.8\text{Hz}$), 7.8 (1H, m), 7.93 (2H, d, $J=8.8\text{Hz}$), 8.07 (2H, d, $J=8.8\text{Hz}$), 8.11 (2H, d, $J=8.8\text{Hz}$), 8.30 (1H, d, $J=7.8\text{Hz}$), 8.67 (1H, m), 8.85 (1H, d, $J=7.8\text{Hz}$)

MASS (m/z): 1465.9 ($\text{M}^+ + \text{Na}$)

Elemental Analysis Calcd. for $\text{C}_{68}\text{H}_{95}\text{N}_{13}\text{O}_{18}\text{S}_2 \cdot 4\text{TFA} \cdot 8\text{H}_2\text{O}$:

C 44.60, H 5.66, N 8.90

Found: C 44.70, H 5.59, N 8.95

Example 121

- 5 IR (KBr): 3355.5, 1635.3, 1533.1, 1515.8, 1417.4,
1257.4 cm^{-1}
- NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.6\text{Hz}$), 1.14 (3H, d,
 $J=5.4\text{Hz}$), 1.2-5.6 (68H, m), 6.71 (1H, d, $J=8.1\text{Hz}$),
6.78 (1H, d, $J=9.5\text{Hz}$), 7.02 (1H, s), 7.14 (2H, d,
10 $J=8.8\text{Hz}$), 7.97 (2H, d, $J=8.7\text{Hz}$), 8.05 (2H, d,
 $J=8.6\text{Hz}$), 8.10 (2H, d, $J=8.5\text{Hz}$), 7.4-9.0 (6H, m)
- MASS (m/z): 1432.4 ($M^+ + \text{Na}$)
- Elemental Analysis Calcd. for $\text{C}_{65}\text{H}_{91}\text{N}_{11}\text{O}_{20}\text{S}_2 \cdot 7\text{H}_2\text{O}$:
C 50.80, H 6.89, N 10.03
- 15 Found: C 50.59, H 6.84, N 10.00

Example 122

- IR (KBr): 3374.8, 1648.8, 1631.5, 1538.9, 1513.8,
1450.2, 1442.5, 1257.4 cm^{-1}
- 20 NMR (DMSO- d_6 , δ): 0.98 (3H, d, $J=6.8\text{Hz}$), 1.0-5.4 (65H,
m), 6.6-6.9 (2H, m), 7.00 (1H, s), 7.14 (2H, d,
 $J=8.4\text{Hz}$), 7.97 (2H, d, $J=8.2\text{Hz}$), 8.05 (2H, d,
 $J=8.7\text{Hz}$), 8.11 (2H, d, $J=8.2\text{Hz}$), 7.3-9.0 (7H, m)
- MASS (m/z): 1429.3 ($M^- - 1$)
- 25 Elemental Analysis Calcd. for $\text{C}_{63}\text{H}_{86}\text{N}_{10}\text{O}_{22}\text{S}_3 \cdot 5\text{H}_2\text{O}$:
C 49.73, H 6.36, N 9.20
- Found: C 49.56, H 6.74, N 9.18

Example 123

- 30 IR (KBr): 2935, 2864, 1649, 1539, 1514, 1450, 1442.5,
1257 cm^{-1}
- NMR (DMSO- d_6 + D_2O , δ): 0.98 (3H, d, $J=6.7\text{Hz}$), 1.12 (3H,
d, $J=5.7\text{Hz}$), 1.2-4.9 (46H, complex m), 3.21 (3H,
s), 3.31 (2H, t, $J=6.4\text{Hz}$), 5.63 (1H, s), 6.7-6.8
35 (2H, m), 7.02 (1H, br s), 7.15 (2H, d, $J=8.8\text{Hz}$),

7.32 (5H, s), 7.97 (2H, d, $J=8.8\text{Hz}$), 8.06 (4H, s)
MASS (m/z): 1460.4 (M^+)

Elemental Analysis Calcd. for $C_{68}H_{88}N_{10}O_{22}S_2 \cdot 6H_2O$:

C 52.03, H 6.42, N 8.92

5

Found: C 51.77, H 6.39, N 8.77

Example 124

IR (KBr): 2935, 1664.3, 1631.5, 1606.4, 1442.5,
1411.6 cm^{-1}

10

NMR (DMSO- d_6 + D_2O , δ): 0.97 (3H, d, $J=6.8\text{Hz}$), 1.07 (3H, d, $J=5.4\text{Hz}$), 1.33 (6H, d, $J=6.3\text{Hz}$), 1.32-4.81 (46H, complex m), 3.21 (3H, s), 3.31 (2H, t, $J=6.5\text{Hz}$), 6.7-6.8 (2H, m), 7.03 (1H, br s), 7.14 (2H, d, $J=8.8\text{Hz}$), 7.98 (2H, d, $J=8.8\text{Hz}$), 8.08 (4H, s)

15

MASS (m/z): 1411.5 (M^+-1)

Elemental Analysis Calcd. for $C_{64}H_{88}N_{10}O_{22}S_2 \cdot 5H_2O$:

C 51.12, H 6.57, N 9.32

Found: C 51.37, H 6.49, N 9.34

20 Example 125

IR (KBr): 3355, 2937, 1673, 1631, 1535, 1515, 1442,
1259, 1201, 1180, 1133, 1087, 1045 cm^{-1}

25

NMR (DMSO- d_6 , δ): 0.98 (3H, d, $J=6.7\text{Hz}$), 1.10 (3H, d, $J=5.7\text{Hz}$), 1.3-1.6 (9H, m), 1.6-2.7 (17H, m), 3.21 (3H, s), 2.8-3.6 (12H, m), 3.6-4.2 (14H, m), 4.2-4.6 (7H, m), 4.83 (3H, m), 5.0 (1H, m), 5.15 (2H, m), 5.30 (2H, m), 6.70 (1H, d, $J=8.2\text{Hz}$), 6.78 (1H, d, $J=8.2\text{Hz}$), 7.05 (1H, s), 7.14 (2H, d, $J=8.8\text{Hz}$), 7.46 (1H, d, $J=8.4\text{Hz}$), 7.57 (1H, d, $J=8.4\text{Hz}$), 7.88 (1H, m), 7.97 (2H, d, $J=8.8\text{Hz}$), 8.05 (2H, d, $J=8.5\text{Hz}$), 8.12 (2H, d, $J=8.5\text{Hz}$), 8.42 (1H, m), 8.7 (1H, m), 8.93 (1H, d, $J=8.4\text{Hz}$)

30

MASS (m/z): 1408.94 (M^+-Na)

Elemental Analysis Calcd. for $C_{66}H_{93}N_{11}O_{21}S_2 \cdot 2TFA \cdot 5H_2O$:

C 47.80, H 6.02, N 8.76

Found: C 47.80, H 6.27, N 8.90

Example 126

5 MASS (m/z): 1612.5 (M^-)+1

Example 127

IR (KBr): 3353.6, 1664.3, 1627.6, 1446.4, 1257.4 cm^{-1}

MASS (m/z): 1454.4 (M^-)-1

10 Elemental Analysis Calcd. for $\text{C}_{86}\text{H}_{93}\text{N}_{11}\text{O}_{22}\text{S}_2 \cdot 7\text{H}_2\text{O}$:

C 50.09, H 6.81, N 9.73

Found: C 49.80, H 6.81, N 9.73

Example 128

15 IR (KBr): 3353.6, 1658.5, 1635.3, 1517.7, 1444.4,
 1255.4 cm^{-1}

MASS (m/z): 1482.4 (M^-)-1

Elemental Analysis Calcd. for $\text{C}_{68}\text{H}_{97}\text{N}_{11}\text{O}_{22}\text{S}_2 \cdot 6\text{H}_2\text{O}$:

C 51.28, H 6.90, N 9.67

20 Found: C 51.57, H 6.80, N 9.68

Example 129

IR (KBr): 3401.8, 1664.3, 1635.3, 1446.4, 1255.4 cm^{-1}

MASS (m/z): 1496.5 (M^-)-1

25

Example 130

major product

IR (KBr): 3351.7, 1658.5, 1635.3, 1517.7, 1444.4,
 1255.4 cm^{-1}

30 MASS (m/z): 1469.5 (M^-)-1

Elemental Analysis Calcd. for $\text{C}_{67}\text{H}_{95}\text{N}_{11}\text{O}_{22}\text{S}_2 \cdot 8\text{H}_2\text{O}$:

C 49.84, H 6.93, N 9.54

Found: C 49.95, H 6.52, N 9.37

35 minor product

IR (KBr): 3351.7, 1664.3, 1635.3, 1529.3, 1517.7,
1446.4, 1255.4 cm^{-1}
MASS (m/z): 1439.5 (M^{-1})

5 Example 131

IR (KBr): 2935, 1649, 1539, 1514, 1452, 1257 cm^{-1}
MASS (m/z): 1563.4 (M^{+1})
Elemental Analysis Calcd. for $\text{C}_{12}\text{H}_{100}\text{N}_{12}\text{O}_{23}\text{S}_2 \cdot 8\text{H}_2\text{O}$:
C 50.58, H 6.84, N 9.83
10 Found: C 50.43, H 6.69, N 9.81

Example 132

MASS (m/z): 1480.4 (M^{+1})

15 Example 133

The object compound (133) was used directly in the next reaction without purification.

Example 134

20 The object compound (134) was used directly in the next reaction without purification.

Example 135

25 The object compound (135) was used directly in the next reaction without purification.

Example 136

IR (KBr): 1659, 1635, 1444, 1257 cm^{-1}
NMR ($\text{DMSO}-d_6$, δ): 0.9-1.25 (6H, m), 1.25-2.6 (23H, m),
30 2.6-5.2 (34H, m), 6.65-6.8 (2H, m), 6.98 (2H, m),
7.13 (2H, d, $J=9.0\text{Hz}$), 7.2-7.8 (3H, m), 7.97 (2H,
d, $J=8.8\text{Hz}$), 7.95-8.2 (5H, m), 8.4-8.8 (2H, m)
MASS (m/z): 1363 (M^{+23})
Elemental Analysis Calcd. for $\text{C}_{59}\text{H}_{80}\text{N}_{12}\text{O}_{20}\text{S}_2 \cdot 11\text{H}_2\text{O}$:

C 46.03, H 6.68, N 10.92

Found: C 45.83, H 6.26, N 10.72

Example 137

- 5 IR (KBr): 1664, 1605, 1446, 1257 cm^{-1}
NMR (DMSO-d_6 , δ): 0.8–1.2 (6H, s), 1.2–2.7 (23H, m),
2.7–5.4 (38H, m), 6.6–7.0 (2H, m), 7.14 (2H, d,
J=8.8Hz), 7.29 (1H, s), 7.51 (1H, s), 7.4–7.9 (3H,
m), 7.97 (2H, d, J=8.8Hz), 8.0–8.3 (5H, m), 8.6–9.0
10 (2H, m)
MASS (m/z): 1391 ($\text{M}^+ - 1$)

The following compounds [Examples 138 to 192] were
obtained according to a similar manner to that of Example 1.

15

Example 138

- IR (KBr): 1666, 1632, 1535, 1514, 1441, 1271 cm^{-1}
NMR ($\text{DMSO-d}_6 + \text{D}_2\text{O}$, δ): 0.98 (3H, d, J=6.72Hz), 1.08
(3H, d, J=5.78Hz), 1.35 (9H, s), 1.45–2.00 (6H, m),
20 2.10–2.40 (3H, m), 2.75–2.95 (3H, m), 3.10–3.40
(2H, m), 3.60–4.50 (14H, m), 4.70–4.80 (2H, m),
6.72 (1H, d, J=8.12Hz), 6.77 (1H, d, J=9.72Hz),
7.02 (1H, s)
ESI MASS (m/z)(Positive): 992 ($\text{M}^+ + 1$)
25 Elemental Analysis Calcd. for $\text{C}_{40}\text{H}_{74}\text{N}_8\text{O}_{25}\text{S} \cdot 6\text{H}_2\text{O}$:
C 43.71, H 6.79, N 10.19
Found: C 43.75, H 6.71, N 10.11

Example 139

- 30 IR (KBr): 3324, 2975, 2937, 1631, 1610, 1529, 1519,
1465, 1446, 1240, 1176, 1085, 1045 cm^{-1}
NMR (DMSO-d_6 , δ): 0.96 (3H, d, J=6.7Hz), 1.10 (3H, d,
J=5.7Hz), 1.18 (6H, d, J=6.2Hz), 1.6–2.1 (3H, m),
2.1–2.6 (6H, m), 2.98 (2H, m), 3.20 (1H, m), 3.4
35 (2H, m), 3.73 (4H, m), 3.8–4.6 (14H, m), 4.6–5.6

(9H, m), 6.70 (1H, d, J=8.2Hz), 6.81 (1H, d, J=8.2Hz), 6.89 (1H, s), 7.04 (1H, s), 7.11 (2H, d, J=8.9Hz), 7.2-7.7 (4H, m), 7.78 (2H, d, J=8.9Hz), 7.95 (4H, s), 8.07 (1H, m), 8.54 (1H, m), 8.80 (1H, s), 8.95 (1H, s)

MASS (m/z): 1321.2 ($M^{+}-1$)

Elemental Analysis Calcd. for $C_{58}H_{74}N_{12}O_{20}S_2 \cdot 10H_2O$:

C 46.33, H 6.30, N 11.18

Found: C 46.26, H 5.98, N 11.04

Example 140

IR (KBr): 3355, 2937, 1633, 1629, 1529, 1517, 1467, 1446, 1253, 1176, 1114, 1083, 1045 cm^{-1}

NMR (DMSO- d_6 , δ): 0.96 (2H, d, J=6.7Hz), 0.96 (3H, d, J=6.7Hz), 1.10 (3H, d, J=5.7Hz), 1.2-1.6 (8H, m), 1.6-2.1 (9H, m), 2.1-2.6 (2H, m), 3.0 (3H, m), 3.40 (2H, m), 3.75 (2H, m), 3.9-4.2 (6H, m), 4.2-4.6 (7H, m), 4.6-4.9 (3H, m), 5.0 (1H, m), 5.2 (2H, m), 5.30 (1H, d, J=4.4Hz), 6.69 (1H, d, J=9.8Hz), 6.78 (1H, d, J=9.8Hz), 7.08 (1H, s), 7.15 (2H, d, J=9.0Hz), 7.41 (1H, d, J=8.8Hz), 7.5 (1H, m), 7.77 (1H, m), 7.88 (2H, d, J=8.8Hz), 7.96 (4H, s), 8.34 (1H, d, J=6.3Hz), 8.75 (1H, d, J=8.5Hz), 8.85 (1H, m), 8.86 (1H, s)

MASS (m/z): 1306.3 ($M^{+}-1$)

Elemental Analysis Calcd. for $C_{58}H_{73}N_{11}O_{20}S_2 \cdot 9H_2O$:

C 47.37, H 6.24, N 10.48

Found: C 47.32, H 6.05, N 10.32

Example 141

IR (KBr): 3328, 2937, 1635, 1529, 1519, 1465, 1444, 1255, 1178, 1112, 1085, 1045 cm^{-1}

NMR (DMSO- d_6 , δ): 0.97 (3H, d, J=6.7Hz), 1.10 (3H, d, J=5.7Hz), 1.2 (2H, m), 1.4-2.1 (14H, m), 2.2-2.5 (3H, m), 2.90 (3H, m), 3.22 (3H, s), 3.75 (2H, m),

3.8-4.2 (9H, m), 4.2-4.6 (6H, m), 4.8 (3H, m), 5.2 (2H, m), 5.3 (1H, m), 6.70 (1H, d, J=8.2Hz), 6.80 (1H, d, J=8.2Hz), 7.08 (1H, s), 7.15 (2H, d, J=8.8Hz), 7.42 (1H, d, J=8.0Hz), 7.5 (2H, m), 7.77 (1H, m), 7.90 (2H, d, J=8.8Hz), 7.96 (4H, s), 8.3 (1H, m), 8.73 (1H, d, J=6.5Hz), 8.86 (1H, s)

MASS (m/z): 1324.3 (M^+-1)

Elemental Analysis Calcd. for $C_{58}H_{75}N_{11}O_{21}S_2 \cdot 9H_2O$:

C 46.80, H 6.30, N 10.35

Found: C 46.66, H 6.13, N 10.12

Example 142

IR (KBr): 1651, 1539, 1514, 1234 cm^{-1}

NMR (DMSO- d_6 , δ): 0.85-1.3 (12H, m), 1.5-2.6 (10H, m), 2.7-3.6 (18H, m), 3.6-5.4 (24H, m), 6.65-7.2 (9H, m), 7.3-8.0 (9H, m), 8.2-8.45 (1H, m), 8.6-8.95 (2H, m)

MASS (m/z): 1358 (M^+-1)

Elemental Analysis Calcd. for $C_{64}H_{85}N_{11}O_{20}S \cdot 7H_2O$:

C 51.73, H 6.71, N 10.36

Found: C 51.50, H 6.70, N 11.31

Example 143

IR (KBr): 2931, 1659, 1633, 1531, 1506, 1444, 1385 cm^{-1}

NMR (DMSO- d_6 , δ): 0.83 (3H, t, J=6.7Hz), 0.96 (3H, d, J=6.8Hz), 1.07 (3H, d, J=5.4Hz), 1.18-1.52 (10H, m), 1.60-2.08 (7H, m), 2.08-2.43 (2H, m), 2.79-3.03 (3H, m), 3.14-3.55 (2H, m), 3.65-4.54 (16H, m), 4.65-5.20 (9H, m), 6.74 (1H, d, J=8.2Hz), 6.83 (1H, d, J=8.5Hz), 6.97 (2H, d, J=8.8Hz), 7.08 (1H, s), 7.40 (1H, d, J=9.2Hz), 7.33-7.86 (2H, m), 7.85 (2H, d, J=8.8Hz), 8.31 (1H, d, J=6.6Hz), 8.58 (1H, d, J=7.8Hz), 8.85 (1H, br s)

MASS (m/z): 1137.4 (M^+-1)

Elemental Analysis Calcd. for $C_{50}H_{74}N_8O_{20}S \cdot 7H_2O$:

C 47.46, H 7.01, N 8.86

Found: C 47.31, H 6.85, N 8.78

Example 144

- 5 IR (KBr): 3344.0, 1672.0, 1658.5, 1664.3, 1635.3,
1446.4, 1257.4 cm^{-1}
ESI MASS (m/z): 1219 ($\text{M}^+ + 1$)

Example 145

- 10 IR (KBr): 2974, 2937, 1633, 1537, 1514, 1443, 1269 cm^{-1}
NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.8\text{Hz}$), 1.13 (3H, d,
 $J=5.6\text{Hz}$), 1.18 (3H, t, $J=7.0\text{Hz}$), 1.35-2.56 (5H, m),
2.56-2.84 (4H, m), 2.84-3.40 (5H, m), 3.52 (2H, q,
 $J=7.0\text{Hz}$), 3.68-4.60 (13H, m), 4.53 (2H, s), 4.60-
15 5.30 (8H, m), 6.71 (1H, d, $J=8.2\text{Hz}$), 6.77 (1H, d,
 $J=8.2\text{Hz}$), 6.96 (1H, s), 7.46 (2H, d, $J=8.3\text{Hz}$), 7.77
(2H, d, $J=8.2\text{Hz}$), 7.58-7.84 (2H, m), 7.92 (2H, d,
 $J=8.5\text{Hz}$), 7.84-8.27 (8H, m), 8.70-8.85 (2H, m)
MASS (m/z): 1287.3 ($\text{M}^+ - 1$)
20 Elemental Analysis Calcd. for $\text{C}_{59}\text{H}_{72}\text{N}_{10}\text{O}_{19}\text{S}_2 \cdot 9\text{H}_2\text{O}$:
C 48.82, H 6.25, N 9.65
Found: C 48.73, H 6.01, N 9.45

Example 146

- 25 IR (KBr): 2939, 1633, 1606, 1535, 1525, 1444, 1419,
1358 cm^{-1}
NMR (DMSO- d_6 , δ): 0.96 (3H, d, $J=6.7\text{Hz}$), 1.13 (3H, d,
 $J=5.6\text{Hz}$), 1.33-2.78 (16H, m), 2.78-5.00 (26H, m),
4.56 (2H, s), 5.00-5.35 (2H, m), 6.70 (1H, d,
30 $J=8.1\text{Hz}$), 6.77 (1H, d, $J=8.1\text{Hz}$), 6.96 (1H, s), 7.10
(2H, d, $J=9.0\text{Hz}$), 7.20-7.80 (8H, m), 7.84 (2H, d,
 $J=8.8\text{Hz}$), 8.06 (4H, s), 8.00-8.30 (1H, m), 8.40-
8.80 (2H, m)
MASS (m/z): 1342.3 ($\text{M}^+ - 1$)
35 Elemental Analysis Calcd. for $\text{C}_{62}\text{H}_{77}\text{N}_{11}\text{O}_{19}\text{S}_2 \cdot 12\text{H}_2\text{O}$:

C 47.72, H 6.52, N 9.87

Found: C 47.98, H 6.00, N 9.72

Example 147

- 5 IR (KBr): 2937, 1633, 1533, 1512, 1443 cm^{-1}
NMR ($\text{DMSO}-d_6$, δ): 0.98 (3H, d, $J=6.8\text{Hz}$), 1.12 (3H, d, $J=5.6\text{Hz}$), 1.60-2.64 (9H, m), 2.01 (2H, t, $J=6.3\text{Hz}$), 2.83-3.03 (3H, m), 3.13-3.60 (2H, m), 3.27 (3H, s), 3.50 (2H, t, $J=6.3\text{Hz}$), 3.68-4.58 (13H, m), 4.09
10 (2H, t, $J=6.4\text{Hz}$), 4.70-5.30 (8H, m), 6.71 (1H, d, $J=8.1\text{Hz}$), 6.78 (1H, dd, $J=8.3$ and 7Hz), 7.01 (1H, d, $J=1.6\text{Hz}$), 7.08 (2H, d, $J=8.8\text{Hz}$), 7.45 (1H, d, $J=8.4\text{Hz}$), 7.57-7.82 (2H, m), 7.73 (2H, d, $J=8.8\text{Hz}$), 7.87 (2H, d, $J=8.5\text{Hz}$), 8.02-8.20 (6H, m), 8.30 (1H, d, $J=6.2\text{Hz}$), 8.71 (1H, br s), 8.93 (1H, d, $J=7.4\text{Hz}$)
15 MASS (m/z): 1317.3 (M^+-1)
Elemental Analysis Calcd. for $\text{C}_{60}\text{H}_{74}\text{N}_{10}\text{O}_{20}\text{S}_2\cdot 8\text{H}_2\text{O}$:
C 49.24, H 6.20, N 9.57
Found: C 48.95, H 6.04, N 9.36
- 20

Example 148

- IR (KBr): 2929, 1633, 1608, 1518, 1444, 1419 cm^{-1}
NMR ($\text{DMSO}-d_6$, δ): 0.86 (3H, d, $J=6.4\text{Hz}$), 0.98 (3H, d, $J=6.8\text{Hz}$), 1.14-1.40 (5H, m), 1.11 (3H, d, $J=5.5\text{Hz}$),
25 1.60-2.74 (18H, m), 1.80-3.02 (3H, m), 3.02-3.58 (6H, m), 3.70-4.60 (13H, m), 4.70-5.40 (8H, m), 6.71 (1H, d, $J=8.2\text{Hz}$), 6.78 (1H, dd, $J=8.1$ and 1.6Hz), 7.01 (1H, d, $J=1.7\text{Hz}$), 7.08 (2H, d, $J=8.7\text{Hz}$), 7.25 (1H, d, $J=8.8\text{Hz}$), 7.57-7.92 (2H, m),
30 7.45 (2H, d, $J=8.4\text{Hz}$), 8.00-8.20 (4H, m), 8.31 (1H, d, $J=6.4\text{Hz}$), 8.71 (1H, br s), 8.91 (1H, d, $J=7.7\text{Hz}$)
MASS (m/z): 1333.4 (M^+-1)
Elemental Analysis Calcd. for $\text{C}_{61}\text{H}_{82}\text{N}_{12}\text{O}_{18}\text{S}_2\cdot 9\text{H}_2\text{O}$:
C 48.92, H 6.73, N 11.22
35 Found: C 49.12, H 6.71, N 11.08

Example 149

IR (KBr): 2933, 2860, 1659, 1630, 1547, 1510, 1446,
1387, 1329 cm^{-1}

- 5 NMR ($\text{DMSO}-d_6$, δ): 0.97 (3H, d, $J=6.8\text{Hz}$), 1.07 (3H, d, $J=5.2\text{Hz}$), 1.26-1.60 (10H, m), 1.60-2.08 (5H, m),
2.18 (6H, s), 2.12-2.67 (4H, m), 2.79-3.03 (3H, m),
3.10-3.50 (12H, m), 3.21 (3H, s), 3.64 (2H, t, $J=6.2\text{Hz}$), 3.64-4.08 (6H, m), 4.12-4.52 (7H, m),
10 4.67-5.26 (8H, m), 6.65 (2H, s), 6.64-6.84 (2H, m),
6.94-7.10 (3H, m), 7.43 (1H, d, $J=8.8\text{Hz}$), 7.34-7.97
(2H, m), 7.80 (2H, d, $J=8.7\text{Hz}$), 8.22-8.40 (1H, m),
8.40-8.59 (1H, m), 8.72 (1H, br s)

MASS (m/z): 1325.6 (M^+-1)

- 15 Elemental Analysis Calcd. for $\text{C}_{62}\text{H}_{90}\text{N}_{10}\text{O}_{20}\text{S}\cdot 6\text{H}_2\text{O}$:
C 51.87, H 7.16, N 9.76
Found: C 51.80, H 7.15, N 9.72

Example 150

- 20 NMR ($\text{DMSO}-d_6$, δ): 0.97 (3H, d, $J=6.9\text{Hz}$), 1.07 (3H, d, $J=5.2\text{Hz}$), 0.80-2.67 (21H, m), 2.77-3.00 (3H, m),
3.08-2.58 (10H, m), 3.52 (2H, t, $J=6.3\text{Hz}$), 3.68-
4.51 (16H, m), 4.70-5.28 (8H, m), 6.68-7.10 (9H,
m), 7.43 (1H, d, $J=8.8\text{Hz}$), 7.56-7.90 (2H, m), 7.80
25 (2H, d, $J=8.8\text{Hz}$), 8.26-8.40 (1H, m), 8.40-8.55 (1H,
m), 8.65-8.80 (1H, m)

MASS (m/z): 1309.5 (M^+-1)

Example 151

- 30 NMR ($\text{DMSO}-d_6$, δ): 0.97 (3H, d, $J=6.8\text{Hz}$), 1.10 (3H, d, $J=6.0\text{Hz}$), 1.39 (9H, s), 1.65-2.83 (22H, m), 1.81-
3.06 (3H, m), 3.20-4.54 (18H, m), 4.69-5.34 (8H,
m), 6.71 (1H, d, $J=8.1\text{Hz}$), 6.78 (1H, dd, $J=8.3$ and
1.8Hz), 6.70-6.90 (1H, m), 6.98-7.14 (3H, m), 7.44
35 (1H, d, $J=8.8\text{Hz}$), 7.68 (2H, d, $J=8.7\text{Hz}$), 7.72 (2H,

d, J=8.3Hz), 7.38-7.86 (2H, m), 7.95 (2H, d, J=8.5Hz), 8.33 (1H, d, J=6.8Hz), 8.70 (1H, br s), 8.75 (1H, d, J=7.7Hz)

MASS (m/z): 1324.5 (M^+-1)

5

Example 152

IR (KBr): 1632, 1514, 1452, 1234 cm^{-1}

NMR (DMSO- d_6 , δ): 0.9-1.3 (12H, m), 1.5-2.6 (11H, m), 2.7-3.6 (18H, m), 3.6-5.3 (23H, m), 6.7-7.2 (9H, m), 7.4-7.55 (1H, m), 7.6-7.85 (7H, m), 7.94 (2H, d, J=8.3Hz), 8.2-8.4 (1H, m), 8.65-8.8 (1H, m)

10

MASS (m/z): 1266 (M^++23)

Elemental Analysis Calcd. for $\text{C}_{64}\text{H}_{85}\text{N}_{11}\text{O}_{19}\text{S}\cdot 7\text{H}_2\text{O}$:

C 52.27, H 6.79, N 10.48

15

Found: C 52.00, H 6.61, N 10.42

Example 153

NMR (DMSO- d_6 , δ): 0.8-1.3 (6H, m), 1.4-2.6 (13H, m), 2.6-3.6 (15H, m), 3.7-5.3 (21H, m), 6.65-6.9 (2H, m), 6.96 (1H, s), 7.15 (2H, d, J=8.3Hz), 7.35-7.8 (7H, m), 7.86 (2H, d, J=8.7Hz), 7.9-8.2 (5H, m), 8.6-8.9 (2H, m)

20

MASS (m/z): 1376 (M^+-23)

25 Example 154

IR (KBr): 3380.6, 1645.0, 1631.5, 1608.3, 1538.9, 1515.8, 1442.5, 1419.4, 1268.9, 1240.0 cm^{-1}

NMR (DMSO- d_6 , δ): 0.98 (3H, d, J=6.8Hz), 1.11 (3H, d, J=5.6Hz), 1.2-5.4 (48H, m), 6.71 (1H, d, J=8.2Hz), 6.7-6.9 (1H, m), 7.01 (1H, d, J=1.8Hz), 7.07 (2H, d, J=9.1Hz), 7.45 (1H, d, J=9.2Hz), 7.5-7.9 (2H, m), 7.83 (2H, d, J=8.9Hz), 8.07 (4H, s), 8.30 (1H, d, J=5.9Hz), 8.5-8.8 (1H, m), 8.90 (1H, d, J=7.8Hz)

30

MASS (m/z): 1236.3 (M^--1)

35

Elemental Analysis Calcd. for $\text{C}_{55}\text{H}_{71}\text{N}_{11}\text{O}_{18}\text{S}_2\cdot 10\text{H}_2\text{O}$:

C 46.57, H 6.47, N 10.86

Found: C 46.74, H 6.12, N 10.75

Example 155

- 5 IR (KBr): 3359.4, 1645.0, 1631.5, 1538.9, 1515.8,
1438.6, 1255.4 cm^{-1}
- NMR (DMSO- d_6 , δ): 0.91 (3H, t, $J=7.1\text{Hz}$), 0.97 (3H, d,
 $J=6.8\text{Hz}$), 1.10 (3H, d, $J=5.8\text{Hz}$), 1.2-5.4 (46H, m),
6.71 (1H, d, $J=8.1\text{Hz}$), 6.7-6.9 (1H, m), 7.00 (1H,
10 d, $J=1.6\text{Hz}$), 7.08 (2H, d, $J=8.9\text{Hz}$), 7.45 (1H, d,
 $J=8.3\text{Hz}$), 7.5-8.1 (3H, m), 7.80 (2H, d, $J=8.4\text{Hz}$),
7.91 (2H, d, $J=8.8\text{Hz}$), 7.98 (2H, d, $J=8.5\text{Hz}$), 8.2
(1H, m), 8.39 (1H, s), 8.79 (1H, d, $J=7.9\text{Hz}$)
- MASS (m/z): 1238.3 (M^- -1)
- 15 Elemental Analysis Calcd. for $\text{C}_{56}\text{H}_{73}\text{N}_9\text{O}_{19}\text{S}_2 \cdot 9\text{H}_2\text{O}$:
C 47.96, H 6.54, N 8.99
Found: C 48.14, H 6.36, N 8.90

Example 156

- 20 IR (KBr): 3355.5, 1635.3, 1529.3, 1517.7, 1434.8,
1255.4 cm^{-1}
- NMR (DMSO- d_6 , δ): 0.87 (3H, t, $J=6.5\text{Hz}$), 0.97 (3H, d,
 $J=6.8\text{Hz}$), 1.11 (3H, d, $J=5.8\text{Hz}$), 1.2-5.4 (52H, m),
6.71 (1H, d, $J=8.1\text{Hz}$), 6.78 (1H, d, $J=9.9\text{Hz}$), 7.00
25 (1H, d, $J=1.6\text{Hz}$), 7.09 (2H, d, $J=9.0\text{Hz}$), 7.45 (1H,
d, $J=8.8\text{Hz}$), 7.5-7.9 (2H, m), 7.97 (2H, d,
 $J=8.5\text{Hz}$), 8.06 (2H, d, $J=8.5\text{Hz}$), 8.29 (1H, d,
 $J=8.9\text{Hz}$), 8.40 (2H, d, $J=8.8\text{Hz}$), 8.81 (1H, d,
 $J=7.4\text{Hz}$), 9.26 (2H, s)
- 30 MASS (m/z): 1275.4 (M^- -1)
- Elemental Analysis Calcd. for $\text{C}_{60}\text{H}_{80}\text{N}_{10}\text{O}_{19}\text{S} \cdot 8\text{H}_2\text{O}$:
C 50.70, H 6.81, N 9.85
Found: C 50.50, H 6.69, N 9.69

Example 157

- IR (KBr): 3361.3, 1631.5, 1511.9, 1446.4, 1267.0,
1232.3, 1045.2 cm^{-1}
- 5 NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.7\text{Hz}$), 1.09 (3H, d, $J=5.8\text{Hz}$), 1.0-5.6 (57H, m), 6.70 (1H, d, $J=8.1\text{Hz}$), 6.7-6.9 (1H, m), 6.92 (2H, d, $J=8.7\text{Hz}$), 6.99 (1H, s), 7.01 (2H, d, $J=9.4\text{Hz}$), 7.09 (2H, d, $J=8.7\text{Hz}$), 7.3-7.9 (3H, m), 7.80 (2H, d, $J=8.8\text{Hz}$), 8.1-8.5 (3H, m)
- 10 MASS (m/z): 1235.4 (M^- -H)
- Elemental Analysis Calcd. for $\text{C}_{58}\text{H}_{80}\text{N}_{10}\text{O}_{18}\text{S}_9\text{H}_2\text{O}$:
C 49.78, H 7.06, N 10.01
Found: C 49.88, H 6.87, N 9.89

15 Example 158

- IR (KBr): 3359.4, 1633.4, 1535.1, 1511.9, 1442.5,
1251.6 cm^{-1}
- 20 NMR (DMSO- d_6 , δ): 0.8-1.1 (6H, m), 1.1-1.3 (3H, m), 1.3-5.6 (42H, m), 6.71 (1H, d, $J=8.1\text{Hz}$), 6.77 (1H, d, $J=9.8\text{Hz}$), 6.97 (1H, s), 7.07 (2H, d, $J=8.9\text{Hz}$), 7.2-9.0 (15H, m)
- MASS (m/z): 1287.4 (M^- -1)

Example 159

- 25 IR (KBr): 3359.4, 1631.5, 1610.3, 1538.9, 1502.3,
1450.2, 1230.4 cm^{-1}
- NMR (DMSO- d_6 , δ): 0.96 (3H, d, $J=6.7\text{Hz}$), 1.0-1.3 (3H, m), 1.3-5.8 (59H, m), 6.70 (1H, d, $J=8.2\text{Hz}$), 6.77 (1H, d, $J=9.9\text{Hz}$), 6.8-7.3 (8H, m), 7.3-9.2 (11H, m)
- 30 MASS (m/z): 1345.5 (M^- -1)

Example 160

MASS (m/z): 1222.3 (M^- -1)

Example 161

IR (KBr): 3353.6, 1631.5, 1537.0, 1517.7, 1467.6,
1440.6, 1272.8, 1045.2 cm^{-1}

5 NMR (DMSO- d_6 , δ): 0.7-1.0 (3H, m), 0.98 (3H, d,
J=6.8Hz), 1.11 (3H, d, J=5.6Hz), 1.2-5.5 (46H, m),
6.71 (1H, d, J=8.1Hz), 6.7-6.9 (1H, m), 7.00 (1H,
d, J=1.6Hz), 7.45 (1H, d, J=8.1Hz), 7.5-8.2 (13H,
m), 8.30 (1H, d, J=7.6Hz), 8.77 (1H, d, J=7.1Hz)

MASS (m/z): 1256.4 (M^{-1})

10 Elemental Analysis Calcd. for $\text{C}_{60}\text{H}_{75}\text{N}_9\text{O}_{19}\text{S}\cdot 8\text{H}_2\text{O}$:

C 51.38, H 6.54, N 8.99

Found: C 51.15, H 6.41, N 8.76

Example 162

15 IR (KBr): 3425.0, 3396.0, 3365.2, 1631.5, 1537.0,
1510.0, 1450.2, 1286.3, 1267.0, 1234.2 cm^{-1}

NMR (DMSO- d_6 , δ): 0.95 (3H, d, J=6.7Hz), 1.10 (3H, d,
J=5.7Hz), 1.3-5.6 (63H, m), 6.7-7.2 (9H, m), 7.3-
7.8 (3H, m), 7.80 (2H, d, J=8.8Hz), 8.0-8.5 (2H, m)

20 MASS (m/z): 1313.4 (M^{-1})

Elemental Analysis Calcd. for $\text{C}_{60}\text{H}_{86}\text{N}_{10}\text{O}_{21}\text{S}\cdot 10\text{H}_2\text{O}$:

C 48.19, H 7.14, N 9.37

Found: C 48.45, H 6.94, N 9.32

25 Example 163

IR (KBr): 1469, 1541, 1514 cm^{-1}

NMR (DMSO- d_6 , δ): 0.7-1.6 (11H, m), 1.6-2.7 (15H, m),
2.7-3.6 (8H, m), 3.6-5.3 (21H, m), 6.7-6.9 (2H, m),
7.00 (1H, s), 7.2-7.9 (5H, m), 7.96 (2H, d,
30 J=8.3Hz), 8.0-8.4 (5H, m), 8.6-9.0 (2H, m)

MASS (m/z): 1235 (M^{+1})

Elemental Analysis Calcd. for $\text{C}_{56}\text{H}_{72}\text{N}_{10}\text{O}_{18}\text{S}_2\cdot 7\text{H}_2\text{O}$:

C 49.33, H 6.36, N 10.27

Found: C 49.07, H 6.40, N 10.02

Example 164IR (KBr): 1633, 1516, 1444, 1255 cm^{-1}

NMR (DMSO- d_6 , δ): 0.9-2.6 (25H, m), 2.7-3.6 (8H, m),
3.6-5.3 (22H, m), 6.65-6.85 (2H, m), 7.00 (1H, s),
7.14 (2H, d, $J=9.0\text{Hz}$), 7.4-8.2 (10H, m), 8.2-8.4
(1H, m), 8.8-9.0 (1H, m)

MASS (m/z): 1251 (M^+-1)Elemental Analysis Calcd. for $\text{C}_{56}\text{H}_{72}\text{N}_{10}\text{O}_{19}\text{S}_2\cdot 8\text{H}_2\text{O}$:

C 48.13, H 6.35, N 10.02

Found: C 48.26, H 6.35, N 9.80

Example 165IR (KBr): 1633, 1518, 1444, 1250 cm^{-1}

NMR (DMSO- d_6 , δ): 0.8-1.6 (15H, m), 1.6-2.6 (11H, m),
2.7-3.6 (8H, m), 3.6-5.3 (23H, m), 6.65-6.85 (2H,
m), 7.00 (1H, s), 7.10 (2H, d, $J=9.0\text{Hz}$), 7.3-8.4
(12H, m), 8.8-9.0 (1H, m), 9.23 (1H, s)

MASS (m/z): 1365 (M^++23)Elemental Analysis Calcd. for $\text{C}_{59}\text{H}_{76}\text{N}_{12}\text{O}_{19}\text{S}_2\cdot 9\text{H}_2\text{O}$:

C 47.77, H 6.39, N 11.33

Found: C 47.67, H 6.19, N 11.20

Example 166IR (KBr): 1662, 1635, 1605, 1444 cm^{-1}

NMR (DMSO- d_6 , δ): 0.8-1.4 (6H, m), 1.5-2.6 (13H, m),
2.6-3.6 (11H, m), 3.6-5.3 (23H, m), 6.65-6.85 (2H,
m), 6.99 (1H, s), 7.05-8.4 (18H, m), 8.8-9.0 (1H,
m)

MASS (m/z): 1312 (M^+-1)Elemental Analysis Calcd. for $\text{C}_{61}\text{H}_{75}\text{N}_{11}\text{O}_{18}\text{S}_2\cdot 9\text{H}_2\text{O}$:

C 49.62, H 6.35, N 10.43

Found: C 49.73, H 6.16, N 10.27

Example 167IR (KBr): 1659, 1628, 1605, 1444 cm^{-1} NMR (DMSO- d_6 , δ): 0.9-2.7 (29H, m), 2.7-5.3 (35H, m),
6.65-6.85 (2H, m), 6.9-7.2 (3H, m), 7.3-7.95 (5H,
5 m), 8.0-8.4 (6H, m), 8.8-9.0 (1H, m)MASS (m/z): 1334 (M^+-1)Elemental Analysis Calcd. for $\text{C}_{61}\text{H}_{81}\text{N}_{11}\text{O}_{19}\text{S}_2\cdot 9\text{H}_2\text{O}$:

C 48.89, H 6.66, N 10.28

Found: C 48.83, H 6.45, N 10.11

10

Example 168IR (KBr): 1659, 1628, 1444 cm^{-1} NMR (DMSO- d_6 , δ): 0.8-2.7 (34H, m), 3.8-3.6 (8H, m),
3.6-5.3 (23H, m), 6.65-6.85 (2H, m), 6.99 (1H, s),
15 7.3-7.85 (5H, m), 7.9-8.4 (7H, m), 8.57 (1H, s),
8.8-9.0 (1H, m)MASS (m/z): 1283 (M^+-1)Elemental Analysis Calcd. for $\text{C}_{57}\text{H}_{80}\text{N}_{12}\text{O}_{18}\text{S}_2\cdot 8\text{H}_2\text{O}$:

C 47.89, H 6.77, N 11.76

Found: C 47.65, H 6.63, N 11.53

20

Example 169IR (KBr): 3324, 2937, 1658, 1629, 1529, 1517, 1465,
1446, 1255, 1178, 1112, 1085, 1045 cm^{-1} NMR (DMSO- d_6 , δ): 0.98 (3H, d, $J=6.7\text{Hz}$), 1.10 (3H, d,
 $J=5.7\text{Hz}$), 1.3-1.6 (4H, m), 1.6-2.1 (4H, m), 2.1-2.5
(3H, m), 2.9 (3H, m), 3.23 (1H, s), 3.38 (2H, m),
3.7-4.6 (19H, m), 4.8 (4H, m), 5.2 (3H, m), 6.71
(1H, d, $J=8.2\text{Hz}$), 6.78 (1H, d, $J=8.2\text{Hz}$), 7.00 (1H,
30 s), 7.15 (2H, d, $J=8.8\text{Hz}$), 7.44 (1H, d, $J=8.5\text{Hz}$),
7.6-7.8 (3H, m), 7.67 (1H, m), 7.90 (2H, d,
 $J=8.8\text{Hz}$), 7.97 (4H, s), 8.34 (1H, d, $J=7.1\text{Hz}$), 8.75
(1H, d, $J=7.5\text{Hz}$), 8.86 (1H, s)MASS (m/z): 1308.3 (M^++1)Elemental Analysis Calcd. for $\text{C}_{58}\text{H}_{75}\text{N}_{11}\text{O}_{20}\text{S}_2\cdot 8\text{H}_2\text{O}$:

35

C 47.89, H 6.31, N 10.59

Found: C 48.02, H 6.21, N 10.49

Example 170

- 5 IR (KBr): 3300, 1635.3, 1510.0, 1232.3 cm^{-1}
NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.8\text{Hz}$), 1.07 (3H, d, $J=5.3\text{Hz}$), 1.72-5.21 (58H, m), 6.69-8.67 (20H, m)
MASS (m/z): 1377.4 ($M^+ + \text{Na}$)
Elemental Analysis Calcd. for $\text{C}_{64}\text{H}_{84}\text{ClN}_{11}\text{O}_{19}\text{S}_6\text{H}_2\text{O}$:
10 C 51.69, H 6.51, N 10.36
Found: C 51.74, H 6.54, N 10.59

Example 171

- 15 IR (KBr): 3347.8, 1631.5, 1610.3, 1510.0, 1230.4 cm^{-1}
NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.9\text{Hz}$), 1.08 (3H, d, $J=4.6\text{Hz}$), 1.70-5.40 (55H, m), 6.67-8.71 (22H, m)
MASS (m/z): 1313.4
Elemental Analysis Calcd. for $\text{C}_{63}\text{H}_{83}\text{N}_{11}\text{O}_{18}\text{S}_4\text{H}_2\text{O}$:
C 54.57, H 6.61, N 11.11
20 Found: C 54.32, H 6.64, N 11.00

Example 172

- IR (KBr): 1659, 1635, 1606, 1529, 1446, 1242 cm^{-1}
NMR (DMSO- d_6 , δ): 0.8-1.3 (12H, m), 1.4-2.6 (11H, m),
25 2.7-3.6 (8H, m), 3.6-5.3 (25H, m), 6.1-6.85 (2H, m), 6.99 (1H, s), 7.11 (2H, d, $J=8.7\text{Hz}$), 7.4-7.85 (3H, m), 7.87 (2H, d, $J=8.9\text{Hz}$), 8.0-8.4 (6H, m), 8.8 (1H, m)
MASS (m/z): 1266 ($M^+ - 1$)
30 Elemental Analysis Calcd. for $\text{C}_{56}\text{H}_{73}\text{N}_{11}\text{O}_{19}\text{S}_2\cdot 10\text{H}_2\text{O}$:
C 46.43, H 6.47, N 10.64
Found: C 46.45, H 5.95, N 10.46

Example 173

IR (KBr): 1659, 1635, 1612, 1512, 1446, 1234 cm^{-1}

NMR (DMSO- d_6 , δ): 0.9-1.3 (12H, m), 1.5-2.4 (11H, m),
2.7-3.6 (18H, m), 3.6-5.3 (23H, m), 6.6-7.1 (9H,
5 m), 7.3-7.9 (6H, m), 8.2-8.5 (2H, m)

MASS (m/z): 1266 (M^+-1)

Elemental Analysis Calcd. for $\text{C}_{58}\text{H}_{81}\text{N}_{11}\text{O}_{19}\text{S}\cdot 7\text{H}_2\text{O}$:

C 49.96, H 6.87, N 11.05

Found: C 49.78, H 6.64, N 10.93

10

Example 174

IR (KBr): 1659, 1628, 1510, 1446, 1236 cm^{-1}

NMR (DMSO- d_6 , δ): 0.7-1.5 (22H, m), 1.5-2.6 (16H, m),
2.7-3.6 (12H, m), 3.6-5.3 (21H, m), 6.6-7.05 (5H,
15 m), 7.3-7.9 (6H, m), 8.2-8.5 (2H, m)

MASS (m/z): 1215 (M^+-1)

Elemental Analysis Calcd. for $\text{C}_{56}\text{H}_{84}\text{N}_{10}\text{O}_{18}\text{S}\cdot 7\text{H}_2\text{O}$:

C 50.06, H 7.35, N 10.43

Found: C 49.95, H 7.19, N 10.30

20

Example 175

IR (KBr): 1630, 1510, 1446, 1238 cm^{-1}

NMR (DMSO- d_6 , δ): 0.7-1.4 (20H, m), 1.6-2.75 (18H, m),
2.75-3.7 (12H, m), 3.7-4.55 (13H, m), 4.6-5.3 (8H,
25 m), 6.6-7.1 (5H, m), 7.3-7.9 (5H, m), 8.2-8.6 (2H,
m), 8.71 (1H, s)

MASS (m/z): 1215 (M^+-1)

Elemental Analysis Calcd. for $\text{C}_{56}\text{H}_{84}\text{N}_{10}\text{O}_{18}\text{S}\cdot 8\text{H}_2\text{O}$:

C 49.40, H 7.40, N 10.29

Found: C 49.45, H 7.28, N 10.20

30

Example 176

IR (KBr): 1664, 1635, 1446, 1240 cm^{-1}

NMR (DMSO- d_6 , δ): 0.7-1.3 (6H, m), 1.4-2.65 (15H, m),
35 2.7-3.6 (12H, m), 3.65-5.3 (21H, m), 6.65-6.85 (2H,

m), 6.9-7.2 (3H, m), 7.3-7.85 (5H, m), 7.9-8.4 (7H, m), 8.7-8.95 (1H, m), 9.17 (1H, s)

MASS (m/z): 1303 (M^+)

Elemental Analysis Calcd. for $C_{58}H_{73}N_{13}O_{18}S \cdot 7H_2O$:

5 C 48.70, H 6.13, N 12.73
Found: C 48.48, H 5.79, N 12.45

Example 177

IR (KBr): 1649, 1632, 1539, 1512, 1454, 1238 cm^{-1}

10 NMR (DMSO- d_6 , δ): 0.8-2.75 (39H, m), 2.75-5.3 (36H, m),
6.65-7.05 (5H, m), 7.3-7.9 (5H, m), 8.2-8.6 (2H, m), 8.71 (1H, s)

MASS (m/z): 1271 (M^+-1)

Elemental Analysis Calcd. for $C_{59}H_{88}N_{10}O_{19}S \cdot 7H_2O$:

15 C 49.99, H 7.39, N 9.88
Found: C 49.80, H 7.21, N 10.11

Example 178

IR (KBr): 1651, 1541, 1512, 1232 cm^{-1}

20 NMR (DMSO- d_6 , δ): 0.8-1.2 (9H, m), 1.4-2.1 (12H, m),
2.1-3.6 (26H, m), 3.6-4.5 (13H, m), 4.6-5.3 (8H, m), 6.6-7.1 (9H, m), 7.3-7.9 (5H, m), 8.2-8.8 (3H, m)

MASS (m/z): 1310 (M^+-1)

25 Elemental Analysis Calcd. for $C_{56}H_{84}N_{10}O_{18}S \cdot 7H_2O$:

C 50.09, H 6.94, N 10.71
Found: C 49.86, H 6.80, N 10.65

Example 179

30 IR (KBr): 1649, 1632, 1539, 1512, 1454, 1238 cm^{-1}

NMR (DMSO- d_6 , δ): 0.8-2.7 (39H, m), 2.7-5.3 (36H, m),
6.65-7.1 (5H, m), 7.3-7.8 (5H, m), 8.25-8.55 (2H, m), 8.70 (1H, s)

MASS (m/z): 1273 (M^++1)

35 Elemental Analysis Calcd. for $C_{59}H_{88}N_{10}O_{19}S \cdot 7H_2O$:

C 50.63, H 7.35, N 10.01

Found: C 50.54, H 7.24, N 9.87

Example 180

- 5 IR (KBr): 1649, 1632, 1541, 1506, 1454, 1232 cm^{-1}
NMR (DMSO- d_6 , δ): 0.9-1.3 (12H, m), 1.6-2.6 (11H, m),
2.6-5.3 (41H, m), 6.7-7.2 (9H, m), 7.3-7.9 (10H,
m), 8.2-8.6 (2H, m)
MASS (m/z): 1342 (M^+-1)
- 10 Elemental Analysis Calcd. for $\text{C}_{64}\text{H}_{85}\text{N}_{11}\text{O}_{19}\text{S}_{10}\text{H}_2\text{O}$:
C 50.42, H 6.94, N 10.11
Found: C 50.71, H 6.82, N 10.03

Example 181

- 15 IR (KBr): 3353.6, 1633.4, 1537.0, 1508.1, 1438.6,
1257.4, 1045.2 cm^{-1}
NMR (DMSO- d_6 , δ): 0.91 (3H, t, $J=7.1\text{Hz}$), 0.98 (3H, d,
 $J=6.8\text{Hz}$), 1.11 (3H, d, $J=5.8\text{Hz}$), 1.2-5.6 (45H, m),
6.71 (1H, d, $J=8.1\text{Hz}$), 6.78 (1H, d, $J=10.0\text{Hz}$), 7.00
20 (1H, s), 7.13 (2H, d, $J=8.9\text{Hz}$), 7.45 (1H, d,
 $J=8.8\text{Hz}$), 7.54 (1H, s), 7.6-8.0 (2H, m), 7.85 (2H,
d, $J=8.7\text{Hz}$), 7.99 (2H, d, $J=8.8\text{Hz}$), 8.05 (2H, d,
 $J=8.6\text{Hz}$), 8.31 (1H, d, $J=7.1\text{Hz}$), 8.71 (1H, s), 8.87
(1H, d, $J=7.1\text{Hz}$)
- 25 MASS (m/z): 1222.3 (M^--1)
Elemental Analysis Calcd. for $\text{C}_{56}\text{H}_{73}\text{N}_9\text{O}_{20}\text{S}_7\text{H}_2\text{O}$:
C 49.81, H 6.49, N 9.33
Found: C 49.99, H 6.43, N 9.30

30 Example 182

- IR (KBr): 3374.8, 1658.5, 1627.6, 1529.3, 1517.7,
1486.8, 1446.4, 1276.6, 1247.7 cm^{-1}
NMR (DMSO- d_6 , δ): 0.91 (3H, t, $J=7.1\text{Hz}$), 0.97 (3H, d,
 $J=6.9\text{Hz}$), 1.12 (3H, d, $J=5.8\text{Hz}$), 1.2-6.5 (46H, m),
35 6.71 (1H, d, $J=8.1\text{Hz}$), 6.77 (1H, d, $J=10.0\text{Hz}$), 6.99

(1H, d, J=1.6Hz), 7.20 (2H, d, J=8.9Hz), 7.46 (1H, d, J=9.5Hz), 7.5-8.3 (3H, m), 8.08 (2H, d, J=8.6Hz), 8.14 (2H, d, J=8.8Hz), 8.17 (2H, d, J=8.4Hz), 8.3-8.8 (1H, m), 8.84 (1H, d, J=7.2Hz)

5 MASS (m/z): 1231.3 (M^{-1})

Elemental Analysis Calcd. for $C_{59}H_{72}N_9NaO_{20}S \cdot 7H_2O$:

C 49.81, H 6.49, N 9.33

Found: C 49.99, H 6.43, N 9.30

10 Example 183

IR (KBr): 3353.6, 1633.4, 1538.9, 1502.3, 1461.8, 1444.4, 1259.3, 1045.2 cm^{-1}

NMR (DMSO- d_6 , δ): 0.91 (3H, t, J=7.1Hz), 0.97 (3H, d, J=7.0Hz), 1.11 (3H, d, J=5.7Hz), 1.2-6.5 (45H, m), 6.71 (1H, d, J=8.2Hz), 6.7-6.9 (1H, m), 6.99 (1H, d, J=1.7Hz), 7.04 (2H, d, J=8.8Hz), 7.45 (1H, d, J=9.0Hz), 7.5-7.9 (10H, m), 8.00 (2H, d, J=8.4Hz), 8.26 (1H, d, J=7.1Hz), 8.3-8.7 (1H, m), 8.73 (1H, d, J=7.9Hz)

20 MASS (m/z): 1223.3 (M^{-1})

Elemental Analysis Calcd. for $C_{59}H_{76}N_9O_{19}S \cdot 6H_2O$:

C 52.83, H 6.61, N 8.35

Found: C 59.91, H 6.54, N 8.32

25 Example 184

IR (KBr): 3353.6, 1658.5, 1633.4, 1232.3 cm^{-1}

NMR (DMSO- d_6 , δ): 0.96 (3H, d, J=6.7Hz), 1.09 (3H, d, J=5.7Hz), 1.50-5.30 (56H, m), 6.68-8.40 (23H, m)

MASS (m/z): 1342.3 (M^{+1})

30 Elemental Analysis Calcd. for $C_{64}H_{85}N_{11}O_{19}S \cdot 7H_2O$:

C 52.27, H 6.79, N 10.48

Found: C 51.98, H 6.47, N 10.59

Example 185IR (KBr): 3347.8, 1633.4, 1511.9, 1230.4 cm^{-1} NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.7\text{Hz}$), 1.07 (3H, d, $J=5.0\text{Hz}$), 1.20-5.22 (66H, m), 6.64-8.56 (17H, m)5 MASS (m/z): 1334.5 ($M^{+}+1$)Elemental Analysis Calcd. for $\text{C}_{63}\text{H}_{89}\text{N}_{11}\text{O}_{19}\text{S}\cdot 7\text{H}_2\text{O}$:

C 51.74, H 7.10, N 10.53

Found: C 52.06, H 6.95, N 10.49

10 Example 186IR (KBr): 3365.2, 1664.3, 1633.4, 1230.4 cm^{-1} NMR (DMSO- d_6 , δ): 0.81-5.25 (78H, m), 6.67-8.53 (14H, m)Elemental Analysis Calcd. for $\text{C}_{61}\text{H}_{92}\text{N}_{10}\text{O}_{19}\text{S}\cdot 12\text{H}_2\text{O}$:

C 48.28, H 7.70, N 9.23

15 Found: C 48.02, H 6.69, N 9.39

Example 187IR (KBr): 3350. 1631.5, 1511.9, 1232.3 cm^{-1} 20 NMR (DMSO- d_6 , δ): 0.96 (3H, d, $J=6.6\text{Hz}$), 1.09 (3H, d, $J=6.0\text{Hz}$), 1.42-5.20 (61H, m), 6.68-8.40 (18H, m)MASS (m/z): 1292.3 ($M^{+}+1$)Elemental Analysis Calcd. for $\text{C}_{61}\text{H}_{85}\text{N}_{11}\text{O}_{18}\text{S}\cdot 7\text{H}_2\text{O}$:

C 51.65, H 7.03, N 10.86

Found: C 51.72, H 6.86, N 10.86

25

Example 188IR (KBr): 1658.5, 1629.6, 1511.9, 1232.3 cm^{-1} NMR (DMSO- d_6 , δ): 0.96 (3H, d, $J=6.5\text{Hz}$), 1.11 (3H, d, $J=5.1\text{Hz}$), 1.51-5.19 (58H, m), 6.68-8.29 (17H, m)30 MASS (m/z): 1294.4 ($M^{+}+1$)Elemental Analysis Calcd. for $\text{C}_{59}\text{H}_{81}\text{N}_{11}\text{O}_{20}\text{S}\cdot 7\text{H}_2\text{O}$:

C 49.82, H 6.73, N 10.83

Found: C 50.33, H 6.42, N 11.00

Example 189

IR (KBr): 3328, 2940, 1664, 1629, 1529, 1519, 1467,
1446, 1257, 1178, 1112, 1085, 1047 cm^{-1}

5 NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.7\text{Hz}$), 1.10 (3H, d,
 $J=5.7\text{Hz}$), 1.5-2.1 (11H, m), 2.2-2.5 (5H, m), 2.90
(3H, m), 3.24 (3H, s), 3.38 (2H, m), 3.4 (2H, m),
3.6-4.6 (18H, m), 4.6-4.9 (3H, m), 5.20 (2H, m),
6.70 (1H, d, $J=8.2\text{Hz}$), 6.80 (1H, d, $J=8.2\text{Hz}$), 7.00
10 (1H, s), 7.15 (2H, d, $J=8.8\text{Hz}$), 7.45 (1H, d,
 $J=8.0\text{Hz}$), 7.7 (3H, m), 7.90 (2H, d, $J=8.8\text{Hz}$), 7.96
(4H, s), 8.3 (1H, m), 8.70 (1H, d, $J=7.8\text{Hz}$), 8.85
(1H, s)

MASS (m/z): 1294.3 (M^+-1)

15 Example 190

IR (KBr): 3324, 2937, 1658, 1635, 1529, 1517, 1465,
1446, 1257, 1178, 1114, 1087, 1045 cm^{-1}

20 NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.7\text{Hz}$), 1.10 (3H, d,
 $J=5.7\text{Hz}$), 1.2-1.6 (6H, m), 1.6-2.1 (4H, m), 2.1-2.5
(3H, m), 2.9 (3H, m), 3.22 (3H, s), 3.38 (2H, m),
3.6-4.3 (14H, m), 4.3-4.6 (5H, m), 4.6-4.9 (4H, m),
5.2 (3H, m), 6.70 (1H, d, $J=8.2\text{Hz}$), 6.78 (1H, d,
 $J=8.2\text{Hz}$), 7.00 (1H, s), 7.14 (2H, d, $J=8.8\text{Hz}$), 7.44
(1H, d, $J=8.2\text{Hz}$), 7.6-7.8 (3H, m), 7.90 (2H, d,
25 $J=8.8\text{Hz}$), 7.96 (4H, s), 8.33 (1H, d, $J=7.1\text{Hz}$), 8.74
(1H, d, $J=7.7\text{Hz}$), 8.86 (1H, s)

MASS (m/z): 1322.4 (M^+-1)

Example 191

30 IR (KBr): 2937, 2864, 1659, 1632, 1510, 1446, 1387,
1327 cm^{-1}

NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.7\text{Hz}$), 1.08 (3H, d,
 $J=5.8\text{Hz}$), 1.22-2.60 (17H, m), 2.79-3.03 (3H, m),
3.10-3.55 (12H, m), 3.21 (3H, s), 3.64-4.08 (6H,
35 m), 3.85 (2H, t, $J=6.5\text{Hz}$), 4.12-4.52 (7H, m), 4.67-

4.90 (6H, m), 5.10-5.25 (2H, m), 6.65-7.08 (9H, m),
7.43 (1H, d, J=8.2Hz), 7.53-7.88 (2H, m), 7.80 (2H,
d, J=8.8Hz), 8.27 (2H, d, J=7.8Hz), 8.44 (1H, d,
J=7.6Hz)

5 MASS (m/z): 1283.4 (M^+-1)

Elemental Analysis Calcd. for $C_{59}H_{84}N_{10}O_{20}S \cdot 5H_2O$:

C 51.52, H 6.89, N 10.18

Found: C 51.51, H 6.96, N 10.09

10 Example 192

IR (KBr): 2935, 2856, 1633, 1533, 1518, 1497, 1446,
1385 cm^{-1}

15 NMR (DMSO- d_6 , δ): 0.97 (3H, d, J=6.7Hz), 1.10 (3H, d,
J=5.4Hz), 1.05-1.38 (6H, m), 1.50-2.14 (9H, m),
2.14-2.43 (2H, m), 2.43-2.67 (7H, m), 2.79-3.03
(3H, m), 3.10-3.50 (6H, m), 3.64-4.08 (6H, m),
4.12-4.52 (7H, m), 4.67-5.26 (8H, m), 6.67-6.84
(2H, m), 6.96-7.10 (1H, m), 7.02 (2H, d, J=8.8Hz),
7.44 (1H, d, J=8.9Hz), 7.61 (2H, d, J=8.8Hz), 7.52-
20 7.50 (2H, m), 7.70 (2H, d, J=8.2Hz), 7.93 (2H, d,
J=8.4Hz), 8.26-8.40 (1H, m), 8.68-8.84 (2H, m)

MASS (m/z): 1235.4 (M^+-1)

Elemental Analysis Calcd. for $C_{58}H_{80}N_{10}O_{18}S \cdot 7H_2O$:

C 51.09, H 6.95, N 10.27

25 Found: C 50.78, H 6.88, N 10.10

Example 193

To a solution of the starting compound (193) (21 mg) in
methanol (1 ml) was added a solution of hydrogen chloride in
30 methanol (0.5 ml), and stirred for 4 hours at ambient
temperature. The reaction mixture was diluted with water,
and subjected to column chromatography on ODS (YMC-gel ODS-
AM-S-50 (Trademark: prepared by Yamamura Chemical Lab.))
eluting with 20% acetonitrile aqueous solution. The
35 fractions containing the object compound were combined, and

evaporated under reduced pressure to remove acetonitrile.
The residue was lyophilized to give the object compound (193)
(19 mg).

IR (KBr): 3355, 2935, 1658, 1635, 1529, 1446, 1255,
1180, 1083, 1006 cm^{-1}
NMR (DMSO- d_6 , δ): 0.98 (3H, d, $J=6.7\text{Hz}$), 1.04 (3H, d,
 $J=5.7\text{Hz}$), 1.2-1.6 (8H, m), 1.6-2.6 (13H, m), 2.6-
3.8 (5H, m), 3.10 (9H, s), 3.21 (3H, s), 3.30 (4H,
t, $J=6.4\text{Hz}$), 3.8-4.7 (12H, m), 4.7-5.0 (3H, m), 5.2
(3H, m), 5.74 (1H, m), 6.38 (1H, d, $J=8.2\text{Hz}$), 6.59
(1H, s), 6.60 (1H, d, $J=8.2\text{Hz}$), 7.14 (2H, d,
 $J=8.8\text{Hz}$), 7.37 (1H, d, $J=9.2\text{Hz}$), 7.53 (1H, d,
 $J=9.2\text{Hz}$), 7.84 (1H, m), 7.97 (2H, d, $J=8.8\text{Hz}$), 8.06
(2H, d, $J=8.8\text{Hz}$), 8.11 (2H, d, $J=8.8\text{Hz}$), 8.67 (2H,
d, $J=4.0\text{Hz}$), 8.85 (1H, d, $J=8.2\text{Hz}$), 8.91 (1H, d,
 $J=8.2\text{Hz}$)
MASS (m/z): 1261.5 (M^+)

The following compounds [Examples 194 to 206] were
obtained according to a similar manner to that of Example
193.

Example 194

IR (KBr): 3353, 2937, 1664, 1627, 1606, 1529, 1446,
1255, 1178, 1112, 1087, 1066, 1006 cm^{-1}
NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.7\text{Hz}$), 1.09 (3H, d,
 $J=5.7\text{Hz}$), 1.2-1.6 (12H, m), 1.6-3.8 (23H, m), 3.21
(3H, s), 3.28 (4H, t, $J=6.4\text{Hz}$), 3.8-4.25 (9H, m),
4.25-4.6 (4H, m), 4.8 (4H, m), 5.1 (1H, m), 5.18
(1H, d, $J=3.0\text{Hz}$), 5.23 (1H, d, $J=5.6\text{Hz}$), 5.40 (1H,
m), 6.39 (1H, d, $J=8.0\text{Hz}$), 6.57 (1H, m), 6.61 (1H,
d, $J=8.0\text{Hz}$), 7.14 (2H, d, $J=8.8\text{Hz}$), 7.42 (1H, d,
 $J=8.8\text{Hz}$), 7.55 (1H, m), 7.80 (1H, m), 7.97 (2H, d,
 $J=8.8\text{Hz}$), 8.07 (2H, d, $J=8.8\text{Hz}$), 8.12 (2H, d,
 $J=8.8\text{Hz}$), 8.57 (1H, d, $J=7.8\text{Hz}$), 8.68 (2H, s), 8.89

(1H, d, J=7.3Hz)

MASS (m/z): 1290.4 (M⁺+1)

Example 195

5 IR (KBr): 3353, 2935, 1658, 1635, 1606, 1529, 1446,
1255, 1180, 1114, 1085, 1062, 1004 cm⁻¹
NMR (DMSO-d₆, δ): 0.97 (3H, d, J=6.7Hz), 1.08 (3H, d,
J=5.7Hz), 1.2-1.6 (10H, m), 1.6-2.6 (21H, m), 2.6-
3.8 (7H, m), 3.21 (3H, s), 3.30 (4H, t, J=6.4Hz),
10 3.8-4.5 (11H, m), 4.8 (3H, m), 5.05 (1H, m), 5.2-
5.3 (2H, m), 5.38 (1H, m), 6.39 (1H, d, J=8.0Hz),
6.57 (1H, m), 6.60 (1H, d, J=8.0Hz), 7.14 (2H, d,
J=8.8Hz), 7.41 (1H, d, J=8.7Hz), 7.45 (1H, d,
J=8.7Hz), 7.87 (1H, d, J=6.8Hz), 7.97 (2H, d,
15 J=8.8Hz), 8.06 (2H, d, J=8.8Hz), 8.12 (21H, d,
J=8.8Hz), 8.60 (1H, d, J=8.0Hz), 8.67 (2H, s), 8.88
(1H, d, J=7.5Hz)
MASS (m/z): 1302.4 (M⁺+1)

20 Example 196

IR (KBr): 3353, 2937, 1664, 1627, 1529, 1446, 1255,
1180, 1114, 1087, 1064, 1006 cm⁻¹
NMR (DMSO-d₆, δ): 0.97 (3H, d, J=6.7Hz), 1.10 (3H, d,
J=5.7Hz), 1.2-1.6 (8H, m), 1.6-2.7 (15H, m), 2.7-
25 3.6 (5H, m), 3.21 (3H, s), 3.6-4.25 (12H, m), 4.25-
4.6 (4H, m), 4.6-5.0 (3H, m), 5.11 (2H, m), 5.35
(1H, m), 6.39 (1H, d, J=8.0Hz), 6.57 (1H, m), 6.61
(1H, d, J=8.0Hz), 7.05 (2H, m), 7.14 (2H, d,
J=8.8Hz), 7.22 (1H, m), 7.44 (1H, d, J=8.9Hz), 7.6-
30 7.8 (2H, m), 7.97 (2H, d, J=8.8Hz), 8.04 (2H, d,
J=8.8Hz), 8.11 (2H, d, J=8.8Hz), 8.39 (1H, d,
J=7.5Hz), 8.68 (1H, m), 8.90 (1H, d, J=6.9Hz)
MASS (m/z): 1261.4 (M⁺+1)

Example 197

IR (KBr): 3349, 2935, 1658, 1635, 1529, 1446, 1255,
1180, 1114, 1087, 1062, 1006 cm^{-1}

5 NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.7\text{Hz}$), 1.13 (3H, d,
 $J=5.7\text{Hz}$), 1.3-1.6 (8H, m), 1.6-2.6 (15H, m), 2.6-
3.6 (8H, m), 3.21 (3H, s), 3.6-4.3 (12H, m), 4.40
(2H, m), 4.55 (1H, m), 4.65 (1H, m), 4.8 (3H, m),
5.16 (3H, m), 6.39 (1H, d, $J=8.0\text{Hz}$), 6.57 (1H, m),
6.62 (1H, d, $J=8.0\text{Hz}$), 7.14 (2H, d, $J=8.8\text{Hz}$), 7.34
10 (1H, m), 7.51 (1H, d, $J=9.2\text{Hz}$), 7.68 (2H, m), 7.97
(2H, d, $J=8.8\text{Hz}$), 8.04 (2H, d, $J=8.8\text{Hz}$), 8.11 (2H,
d, $J=8.8\text{Hz}$), 8.20 (1H, d, $J=6.7\text{Hz}$), 8.57 (1H, m),
8.68 (2H, m), 8.86 (1H, d, $J=7.6\text{Hz}$), 9.14 (1H, s),
9.40 (1H, m)
15 MASS (m/z): 1303.3 ($M^+ + 1$)

Example 198

IR (KBr): 3353.6, 1658.5, 1635.3, 1529.3, 1444.4,
1255.4 cm^{-1}

20 NMR (DMSO- d_6 , δ): 0.98 (3H, d, $J=6.8\text{Hz}$), 1.08 (3H, d,
 $J=5.6\text{Hz}$), 1.2-5.6 (68H, m), 6.40 (1H, d, $J=8.0\text{Hz}$),
6.58 (1H, s), 6.60 (1H, d, $J=8.1\text{Hz}$), 7.14 (2H, d,
 $J=8.9\text{Hz}$), 7.97 (2H, d, $J=8.7\text{Hz}$), 8.08 (2H, d,
 $J=10.8\text{Hz}$), 8.13 (2H, d, $J=8.9\text{Hz}$), 7.3-9.2 (7H, m)
25 MASS (m/z): 1330.4 ($M^+ - \text{Cl}$)

Example 199

IR (KBr): 3349, 2937, 1658, 1627, 1604, 1529, 1446,
1255, 1201, 1114, 1083, 1062, 1006 cm^{-1}

30 NMR (DMSO- d_6 , δ): 0.97 (3H, d, $J=6.7\text{Hz}$), 1.10 (3H, d,
 $J=5.7\text{Hz}$), 1.1-1.5 (10H, m), 1.6-2.6 (17H, m), 2.6-
3.8 (12H, m), 3.8-4.3 (10H, m), 4.4 (4H, m), 4.78
(2H, m), 5.3 (1H, m), 6.39 (1H, d, $J=8.0\text{Hz}$), 6.57
(1H, m), 6.60 (1H, d, $J=8.0\text{Hz}$), 7.20 (2H, d,
35 $J=9.0\text{Hz}$), 7.45 (1H, m), 7.73 (3H, m), 7.86 (2H, d,

J=8.8Hz), 7.97 (4H, s), 8.42 (1H, d, J=6.7Hz), 8.73 (1H, d, J=6.7Hz), 8.84 (1H, s), 10.35 (1H, m)

MASS (m/z): 1280.4 ($M^+ + 1$)

5 Example 200

IR (KBr): 3349, 2935, 1658, 1627, 1606, 1529, 1446, 1251, 1201, 1114, 1085, 1064, 1006 cm^{-1}

NMR (DMSO- d_6 , δ): 0.97 (3H, d, J=6.7Hz), 1.09 (3H, d, J=5.7Hz), 1.1-1.7 (7H, m), 1.7-2.7 (15H, m), 2.7-3.8 (15H, m), 3.8-4.3 (12H, m), 4.45 (4H, m), 4.75 (2H, m), 5.42 (1H, m), 6.39 (1H, d, J=8.0Hz), 6.57 (1H, m), 6.60 (1H, d, J=8.0Hz), 7.18 (2H, d, J=9.0Hz), 7.45 (1H, d, J=8.6Hz), 7.73 (3H, m), 7.92 (2H, d, J=8.8Hz), 8.08 (4H, s), 8.41 (1H, d, J=6.7Hz), 8.89 (1H, d, J=6.7Hz), 10.6 (1H, m)

MASS (m/z): 1241.5 ($M^+ + 1$)

Example 201

IR (KBr): 3347, 2937, 1658, 1635, 1531, 1506, 1444, 1255, 1180, 1114, 1085, 1060, 1006 cm^{-1}

NMR (DMSO- d_6 , δ): 0.8-1.0 (6H, m), 1.10 (3H, d, J=5.7Hz), 1.2-1.6 (5H, m), 1.6-2.7 (11H, m), 2.7-3.1 (4H, m), 3.1-4.3 (12H, m), 4.3-4.6 (5H, m), 4.6-4.9 (4H, m), 4.9-5.4 (5H, m), 6.39 (1H, d, J=8.2Hz), 6.56 (1H, s), 6.61 (1H, d, J=8.2Hz), 7.13 (2H, d, J=8.8Hz), 7.40 (1H, m), 7.3-7.5 (2H, m), 7.74 (1H, m), 7.85 (2H, d, J=8.8Hz), 8.00 (2H, d, J=8.8Hz), 8.06 (2H, d, J=8.8Hz), 8.41 (1H, m), 8.69 (2H, m), 8.88 (1H, d, J=7.0Hz)

MASS (m/z): 1144.3 ($M^+ + 1$)

Example 202

IR (KBr): 3322, 2935, 1664, 1627, 1606, 1529, 1446, 1255, 1201, 1114, 1085, 1064, 1006 cm^{-1}

NMR (DMSO- d_6 , δ): 0.88 (3H, d, J=7.0Hz), 0.97 (3H, d,

J=6.7Hz), 1.10 (3H, d, J=5.7Hz), 0.8-1.2 (2H, m),
1.2-1.6 (5H, m), 1.6-2.0 (6H, m), 2.0-2.7 (9H, m),
2.7-3.1 (4H, m), 3.1-3.8 (9H, m), 3.8-4.3 (8H, m),
4.3-4.6 (4H, m), 4.6-4.9 (3H, m), 4.95 (1H, m),
5
5.12 (1H, d, J=7.3Hz), 5.3-5.4 (3H, m), 6.39 (1H,
d, J=8.0Hz), 6.57 (1H, s), 6.61 (1H, d, J=8.0Hz),
7.19 (2H, d, J=8.9Hz), 7.44 (1H, d, J=9.8Hz), 7.7
(1H, m), 7.93 (2H, d, J=8.8Hz), 8.08 (4H, s), 8.41
(1H, m), 8.70 (2H, s), 8.91 (1H, d, J=6.6Hz), 10.10
10 (1H, m)
MASS (m/z): 1255.4 (M⁺+1)

Example 203

IR (KBr): 3344, 2940, 1658, 1627, 1531, 1496, 1246,
1180, 1114, 1083, 1062, 1004 cm⁻¹
15 NMR (DMSO-d₆, δ): 0.97 (3H, d, J=6.7Hz), 1.09 (3H, d,
J=5.7Hz), 1.1-1.5 (8H, m), 1.65 (2H, m), 1.7-2.0
(6H, m), 2.1-2.7 (7H, m), 2.8-3.1 (4H, m), 3.1-3.8
(9H, m), 3.97 (7H, m), 4.16 (2H, d, J=6.5), 4.23
20 (1H, m), 4.4 (5H, m), 4.75 (3H, m), 4.98 (1H, m),
5.27 (1H, m), 6.39 (1H, d, J=8.0Hz), 6.57 (1H, m),
6.61 (1H, d, J=8.0Hz), 7.12 (2H, d, J=8.8Hz), 7.44
(1H, d, J=8.8Hz), 7.68 (2H, d, J=8.8Hz), 7.72 (2H,
d, J=8.8Hz), 7.6-7.9 (3H, m), 7.96 (2H, d,
25 J=8.8Hz), 8.42 (1H, m), 8.74 (1H, d, J=6.8Hz),
10.06 (1H, m)
MASS (m/z): 1157.6 (M⁺+1)

Example 204

IR (KBr): 3320, 2933, 1658, 1629, 1610, 1510, 1446,
1255, 1234, 1114, 1087, 1064, 1006 cm⁻¹
30 NMR (DMSO-d₆, δ): 0.96 (3H, d, J=6.7Hz), 1.06 (3H, d,
J=5.7Hz), 1.2-1.5 (11H, m), 1.5-1.8 (3H, m), 1.8-
2.1 (5H, m), 2.1-2.7 (6H, m), 2.8-3.1 (4H, m), 3.1-
35 3.8 (13H, m), 3.21 (3H, s), 3.8-4.1 (7H, m), 3.90

- (2H, d, J=6.4Hz), 3.95 (1H, m), 4.2-4.5 (5H, m),
4.75 (3H, m), 5.24 (1H, m), 6.39 (1H, d, J=8.0Hz),
6.57 (1H, m), 6.60 (1H, d, J=8.0Hz), 6.91 (2H, d,
J=8.8Hz), 7.03 (2H, d, J=8.8Hz), 7.17 (1H, m), 7.42
5 (1H, d, J=8.4Hz), 7.72 (5H, m), 7.83 (2H, d,
J=8.4Hz), 8.43 (1H, m), 8.50 (1H, d, J=6.7Hz)
MASS (m/z): 1233.4 ($M^+ + 1$)

Example 205

- 10 IR (KBr): 1651, 1539, 1514, 1234 cm^{-1}
NMR (DMSO- d_6 , δ): 0.85 (9H, s), 0.8-1.3 (11H, m),
1.3-2.4 (13H, m), 2.4-5.4 (40H, m), 6.39 (1H, d,
J=7.5Hz), 6.5-6.7 (2H, m), 7.04 (2H, d, J=8.6Hz),
7.3-8.0 (5H, m), 8.3-8.9 (3H, m), 9.9-10.1 (1H, m)
15 MASS (m/z): 1137 ($M^+ + 1$)
Elemental Analysis Calcd. for $\text{C}_{56}\text{H}_{84}\text{N}_{10}\text{O}_{15} \cdot 3\text{HCl} \cdot 8\text{H}_2\text{O}$:
C 48.36, H 7.46, N 10.07
Found: C 48.25, H 7.20, N 9.81

Example 206

- 20 IR (KBr): 1699, 1678, 1651, 1539, 1514, 1456 cm^{-1}
MASS (m/z): 1264 ($M^+ + 1$)

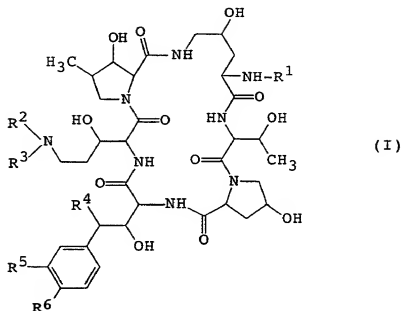
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30

35

C L A I M S

1. A polypeptide compound of the following general formula (I):



wherein

- R¹ is hydrogen or acyl group,
 R² and R³ are independently hydrogen, lower alkyl which may have one or more suitable substituent(s), acyl group, heterocyclic group which may have one or more suitable substituent(s), lower alkylidenyl which may have one or more suitable substituent(s), higher alkyl which may have one or more suitable substituent(s) or cyano,
 R⁴ is hydrogen or hydroxy,
 R⁵ is hydrogen, hydroxy, lower alkoxy or hydroxysulfonyloxy, and
 R⁶ is hydroxy or acyloxy,
 or a salt thereof.

2. A compound of claim 1, wherein

R^2 and R^3 are independently hydrogen;

lower alkyl which may have one or more suitable
5 substituent(s) selected from the group consisting of
amino, carboxy, sulfinic acid group, sulfonic acid
group, hydroxy(lower)alkylamino which may have
hydroxy(lower)alkyl, hydroxysulfonyloxy, imino, lower
alkoxy, oxo, lower alkylthio, cyano(lower)alkylidene,
10 and heterocyclic group which may have one or more lower
alkyl;

lower alkoxy carbonyl which may have one or more
suitable substituent(s) selected from the group
consisting of lower alkanoyloxy and heterocyclic group;

15 lower alkenyloxy carbonyl;

ar(lower)alkoxy carbonyl;

lower alkanoyl which may have one or more suitable
substituent(s) selected from the group consisting of
amino, hydroxy and heterocyclic group;

20 heterocyclic carbonyl;

mono or di(lower)alkyl carbamoyl;

sulfonic acid group;

heterocyclic group which may have one or more
suitable substituent(s) selected from the group
25 consisting of lower alkyl, hydroxy(lower)alkyl,
carboxy(lower)alkanoyl which may have amino,
heterocyclic carbonyl, cyclo(lower)alkyl, and oxo;

lower alkylidene which may have mono or di lower
alkylamino;

30 carboxy(higher)alkyl or
cyano.

3. A compound of claim 2, wherein

R^2 and R^3 are independently hydrogen;

(C₁-C₆)alkyl which may have 1 or 2 suitable substituent(s) selected from the group consisting of amino, carboxy, sulfinic acid group, sulfonic acid group, hydroxy(C₁-C₄)alkylamino which may have
5 hydroxy(C₁-C₄)alkyl, hydroxysulfonyloxy, imino, (C₁-C₄)alkoxy, oxo, cyano(C₂-C₄)alkylidene, (C₁-C₄)alkylthio, and pyrazolyl which may have (C₁-C₄)alkyl;

(C₁-C₄)alkoxycarbonyl which may have (C₁-C₄)-
10 alkanoyloxy, dioxacyclo(C₄-C₆)alkenyl which may have oxo, and (C₁-C₄)alkyl;

fluorenyl(C₁-C₄)alkoxycarbonyl;

(C₂-C₄)alkenyloxy carbonyl;

(C₁-C₆)alkanoyl which may have 1 or 2 suitable
15 substituent(s) selected from the group consisting of amino, hydroxy and pyrazolyl;

pyrrolidinyl carbonyl;

morpholinocarbonyl;

mono or di(C₁-C₄)alkyl carbamoyl;

20 sulfonic acid group;

piperidyl which may have 1 or 2 suitable substituent(s) selected from the group consisting of (C₁-C₄)alkyl, hydroxy(C₁-C₄)alkyl, carboxy(C₁-C₄)-
alkanoyl which may have amino, and azetidiny carbonyl;

25 dioxacyclo(C₄-C₆)alkyl which may have 1 or 2 suitable substituent(s) selected from the group consisting of (C₁-C₄)alkyl, and cyclo(C₄-C₆)alkyl;

thiopyranlyl which may have 1 or 2 oxo;

(C₂-C₄)alkylidene which may have mono or

30 di(C₁-C₄)alkylamino;
carboxy(C₇-C₁₄)alkyl or
cyano.

4. A compound of claim 3, wherein

R² and R³ are independently hydrogen, methyl, aminoethyl, aminobutyl, aminopentyl, carboxymethyl, carboxyethyl, carboxypentyl, sulfonylmethyl, hydroxysulfonylpropyl, hydroxysulfonylbutyl, dihydroxyisopropylaminobutyl, hydroxysulfonyloxypropyl, 1-iminomethoxypropyl, 1-iminocarbamoylethyl, amidino, 2-cyano-1-methylthiovinyl, 2-cyano-1-aminovinyl, methylpyrazolylmethyl, tert-butoxycarbonyl, acetyloxymethoxycarbonyl, 1,3-dioxo-2-oxo-4-methylcyclopentenylmethoxycarbonyl, allyloxycarbonyl, fluorenylmethoxycarbonyl, acetyl, aminopropionyl, aminovaleryl, diaminohexanoyl, 2-hydroxy-4-aminovaleryl, 2-amino-3-pyrazolylpropionyl, pyrrolidinylcarbonyl, morpholinocarbonyl, dimethylcarbamoyl, diethylcarbamoyl, hydroxysulfonyl, piperidyl, dimethylpiperidyl, hydroxyethylmethylpiperidyl, carboxypropionylpiperidyl, 4-amino-4-carboxybutyrylpiperidyl, azetidiny carbonylpiperidyl, dimethyl-1,3-dioxacyclohexyl, cyclohexyl-1,3-dioxacyclohexyl, dioxothiopyranyl, dimethylaminomethylidene, carboxyheptyl or cyano.

5. A compound of claim 1, wherein

R¹ is hydrogen; lower alkoxy carbonyl;

aryloxy which has heterocyclic group substituted with aryl having a suitable substituent selected from the group consisting of lower alkoxy, lower alkoxy(lower)alkoxy, lower alkoxy(higher)alkoxy, aryl substituted with lower alkoxy(lower)alkoxy, cyclo(lower)alkyl, cyclo(lower)alkyloxy, aryl substituted with lower alkoxy, aryl substituted with lower alkoxy(lower)alkyl, aryl substituted with

- heterocyclic group, heterocyclic group substituted with cyclo(lower)alkyl, heterocyclic group, heterocyclic group substituted with aryl, heterocyclic group substituted with aryloxy, heterocyclic group substituted with ar(lower)alkoxy, heterocyclic group substituted with lower alkoxy and aryl, higher alkoxy, heterocyclic(higher)alkoxy, lower alkoxy(higher)alkylsulfonyl, aryloxy(lower)alkoxy, heterocyclic group substituted with
- 5 cyclo(lower)alkyloxy, heterocyclic group substituted with aryl having lower alkoxy(lower)alkoxy, heterocyclic group substituted with lower alkylthio, heterocyclic group substituted with lower alkoxy(lower)alkylthio, and heterocyclic group substituted with lower
- 10 alkoxy(lower)alkoxy;
- aryl which has aryl substituted with a suitable substituent selected from the group consisting of lower alkoxy having cyclo(lower)alkyl and amino, lower alkoxy having cyclo(lower)alkyl and protected amino, aryl
- 20 having lower alkoxy, heterocyclic group having lower alkyl, heterocyclic group having cyclo(lower)alkyl, and heterocyclic group having aryl substituted with heterocyclic group;
- aryl which has heterocyclic group substituted with
- 25 cyclo(lower)alkyl having one or more suitable substituent(s) selected from the group consisting of lower alkyl, lower alkoxy, cyclo(lower)alkyl, and cyclo(lower)alkyl substituted with lower alkoxy;
- higher alkanoyl;
- 30 aroyl which has higher alkoxy; or
- heterocycliccarbonyl which has a suitable substituent(s) selected from the group consisting of heterocyclic group substituted with higher alkyl, heterocyclic group substituted with aryl having lower
- 35 alkoxy, heterocyclic group substituted with aryl having

heterocyclic group, and aryl substituted with lower alkoxy(higher)alkoxy.

6. A compound of claim 5, wherein

5 R^1 is hydrogen; (C_1-C_4) alkoxycarbonyl;

benzoyl which has thiazolyl substituted with phenyl having (C_4-C_6) alkoxy;

10 benzoyl which has thiadiazolyl substituted with phenyl having a suitable substituent selected from the group consisting of (C_1-C_4) alkoxy (C_4-C_6) alkoxy, phenyl substituted with (C_1-C_4) alkoxy (C_1-C_4) alkoxy, (C_1-C_4) alkoxy (C_7-C_{14}) alkoxy, cyclo (C_4-C_6) alkyl, cyclo (C_4-C_6) alkyloxy, phenyl substituted with (C_1-C_4) -alkoxy, phenyl substituted with (C_1-C_4) alkoxy (C_1-C_4) -alkyl, phenyl substituted with di (C_1-C_4) -alkylmorpholino, piperazinyl substituted with cyclo- (C_4-C_6) alkyl, piperazinyl substituted with cyclo- (C_4-C_6) alkyl having (C_1-C_4) alkyl; piperidyl, piperidyl substituted with phenyl, piperidyl substituted with phenoxy, piperidyl substituted with benzyloxy, piperidyl substituted with (C_1-C_4) alkoxy and chlorophenyl, and phenyl having di (C_1-C_4) alkylmorpholino;

20 benzoyl which has pyrimidinyl substituted with phenyl having (C_7-C_{14}) alkoxy;

25 benzoyl which has isoxazolyl substituted with phenyl having a suitable substituent selected from the group consisting of (C_4-C_6) alkoxy, (C_1-C_4) alkoxy- (C_4-C_6) alkoxy, (C_1-C_4) alkoxy (C_7-C_{14}) alkoxy, (C_7-C_{14}) -alkoxy substituted with di (C_1-C_4) alkylmorpholino, and di (C_1-C_4) alkylmorpholino;

30 benzoyl which has oxadiazolyl substituted with phenyl having a suitable substituent selected from the group consisting of (C_4-C_6) alkoxy,

35 (C_1-C_4) alkoxy (C_7-C_{14}) alkoxy, (C_1-C_4) alkoxy (C_7-C_{14}) -alkoxy, and (C_1-C_4) alkoxy (C_7-C_{14}) alkylsulfonyl;

benzoyl which has piperazinyl substituted with phenyl having a suitable substituent selected from the group consisting of (C₁-C₄)alkoxy(C₄-C₆)alkoxy, (C₁-C₄)alkoxy(C₇-C₁₄)alkoxy, phenoxy(C₁-C₄)alkoxy, 5 cyclo(C₄-C₆)alkyl, phenyl substituted with (C₁-C₄)-alkoxy(C₄-C₆)alkoxyphenyl, phenyl substituted with di(C₁-C₄)alkylmorpholino, piperidyl substituted with cyclo(C₄-C₆)alkoxy, piperidyl substituted with phenyl, piperidyl substituted with (C₁-C₄)alkoxy(C₁-C₄)- 10 alkoxyphenyl, piperidyl substituted with (C₁-C₄)alkylthio, piperidyl substituted with (C₁-C₄)alkoxy(C₄-C₆)alkylthio, piperidyl substituted with cyclo(C₄-C₆)alkanespiro, piperidyl substituted with dioxacyclo(C₄-C₆)alkanespiro, piperidyl substituted with 15 (C₁-C₄)alkoxy and phenyl, piperidyl substituted with (C₁-C₄)alkoxy and chlorophenyl, and di(C₁-C₄)-alkylmorpholino;

benzoyl which has piperazinyl substituted with cyclo(C₄-C₆)alkyl having a suitable substituent selected 20 from the group consisting of cyclo(C₄-C₆)-alkyl, (C₄-C₆)alkyl, cyclo(C₄-C₆)alkyl and (C₁-C₄)-alkoxy, and cyclo(C₄-C₆)alkyl substituted with (C₁-C₄)-alkoxy;

benzoyl which has imidazothiadiazolyl substituted 25 with phenyl having a suitable substituent selected from the group consisting of (C₄-C₆)alkoxy, (C₁-C₄)alkoxy-(C₄-C₆)alkoxy, cyclo(C₄-C₆)alkoxy, piperazinyl substituted with cyclo(C₄-C₆)alkyl, piperidyl substituted with (C₁-C₄)alkoxy(C₁-C₄)alkoxy, piperidyl 30 substituted with (C₁-C₄)alkoxy(C₄-C₆)alkoxy, piperidyl substituted with (C₁-C₄)alkoxy(C₄-C₆)alkylthio, and di(C₁-C₄)alkylmorpholino;

benzoyl which has phenyl substituted with a 35 suitable substituent selected from the group consisting of (C₁-C₄)alkoxy having cyclo(C₄-C₆)alkyl and (C₁-C₄)-

alkoxycarbonylamino, (C₁-C₄)alkoxy having cyclo(C₄-C₆)-alkyl and amino, phenyl having (C₄-C₆)alkoxy, thiazolyl having (C₄-C₆)alkyl, piperazinyl having cyclo(C₄-C₆)-alkyl, piperazinyl having phenyl substituted with di(C₁-C₄)alkylmorpholino, and benzoxazolyl having (C₄-C₆)alkyl;

benzoyl which has (C₇-C₁₄)alkoxy;

thiadiazolylcarbonyl which has pyrazolyl substituted with a suitable substituent selected from the group consisting of (C₇-C₁₄)alkyl, phenyl having (C₄-C₆)alkoxy, and phenyl having piperidyl;

piperazinylcarbonyl which has xyllyl substituted with (C₁-C₄)alkoxy(C₇-C₁₄)alkoxy; or (C₇-C₁₄)alkanoyl.

7. A compound of claim 6, wherein R¹ is hydrogen;

benzoyl which has thiazolyl substituted with phenyl having pentyloxy;

benzoyl which has thiadiazolyl substituted with phenyl having a suitable substituent selected from the group consisting of methoxyhexyloxy, methoxyoctyloxy, phenyl substituted with methoxyethoxy, phenyl substituted with methoxybutoxy, methoxyheptyloxy, cyclohexyl, cyclohexyloxy, phenyl substituted with propoxy, phenyl substituted with ethoxymethyl, phenyl substituted with methoxypropoxy, phenyl substituted with dimethylmorpholino, piperazinyl substituted with cyclohexyl, piperazinyl substituted with methylcyclohexyl, piperidyl, piperidyl substituted with phenyl piperidyl substituted with phenoxy, piperidyl substituted with benzyloxy, piperidyl substituted with methoxy and chlorophenyl, and dimethylmorpholino;

benzoyl which has pyrimidinyl substituted with phenyl having octyloxy;

benzoyl which has isoxazolyl substituted with phenyl having a suitable substituent selected from the group consisting of pentyloxy, methoxyhexyloxy, phenyl having methoxyheptyloxy, heptyloxy substituted with dimethylmorpholino, octyloxy substituted with dimethylmorpholino, and dimethylmorpholino;

benzoyl which has oxadiazolyl substituted with phenyl having a suitable substituent selected from the group consisting of pentyloxy, methoxyheptyloxy, methoxynonyloxy, methoxyheptylsulfonyl, and methoxynonylsulfonyl;

benzoyl which has piperazinyl substituted with phenyl having a suitable substituent selected from the group consisting of methoxyhexyloxy, methoxyheptyloxy, phenoxypropoxy, cyclohexyl, phenyl substituted with methoxypentyloxyphenyl, phenyl substituted with dimethylmorpholino, piperidyl substituted with cyclohexyloxy, piperidyl substituted with phenyl, piperidyl substituted with methoxybutoxyphenyl, piperidyl substituted with propylthio, piperidyl substituted with methoxyhexylthio, piperidyl substituted with cyclobutanespiro, piperidyl substituted with dioxacyclobutanespiro, piperidyl substituted with methoxy and phenyl, piperidyl substituted with methoxy and chlorophenyl, and dimethylmorpholino;

benzoyl which has piperazinyl substituted with cyclohexyl having a suitable substituent selected from the group consisting of tert-butyl, cyclohexyl and methoxy, and cyclohexyl substituted with propoxy;

benzoyl which has imidazothiadiazolyl substituted with phenyl having a suitable substituent selected from the group consisting of methoxybutoxy, cyclohexyloxy, piperazinyl substituted with cyclohexyl, piperidyl substituted with methoxypropoxy, piperidyl substituted with methoxybutoxy, piperidyl substituted with

methoxypropyloxy, piperidyl substituted with
methoxyhexyloxy, piperidyl substituted with
methoxyhexylthio, and dimethylmorpholino;

benzoyl which has phenyl substituted with a
suitable substituent selected from the group consisting
of propoxy having cyclohexyl and tert-
butoxycarbonylamino, cyclohexyl and amino, phenyl having
pentyloxy, thiazolyl having pentyl, piperazinyl having
cyclohexyl, piperazinyl having phenyl substituted with
dimethylmorpholino, and benzoxazolyl having pentyl;

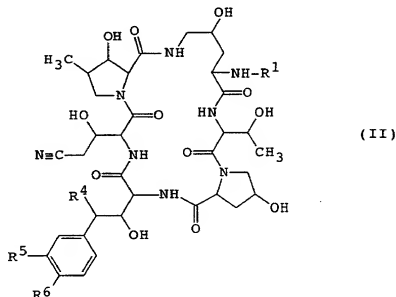
benzoyl which has octyloxy;

thiadiazolylcarbonyl which has pyrazolyl
substituted with a suitable substituent selected from
the group consisting of decyl, phenyl having hexyloxy,
and phenyl having piperidyl;

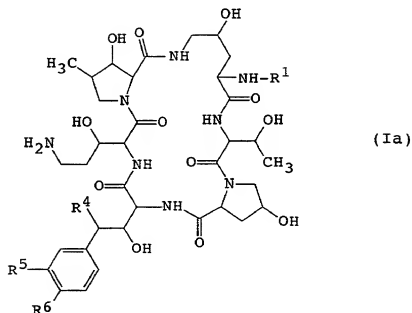
piperazinylcarbonyl which has xylyl substituted
with methoxyheptyloxy; or
palmitoyl.

8. A process for preparing a polypeptide compound (I) of
claim 1, or a salt thereof,
which comprises,

i) reducing a compound (II) of the formula:

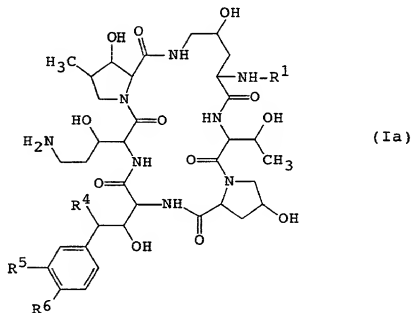


wherein R^1 , R^4 , R^5 and R^6 are as defined in claim 1,
or a salt thereof, to give a compound (Ia) of the
formula:

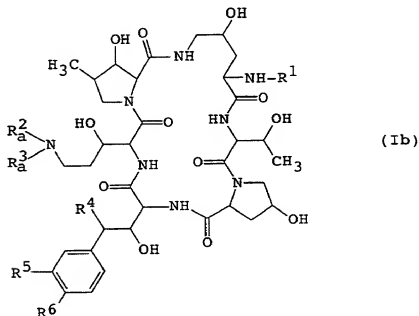


wherein R^1 , R^4 , R^5 and R^6 are as defined in claim 1,
or a salt thereof, or

ii) subjecting a compound (Ia) of the formula:



wherein R^1 , R^4 , R^5 and R^6 are as defined in claim 1, or a salt thereof, to protective reaction of amino, to give a compound (Ib) of the formula:



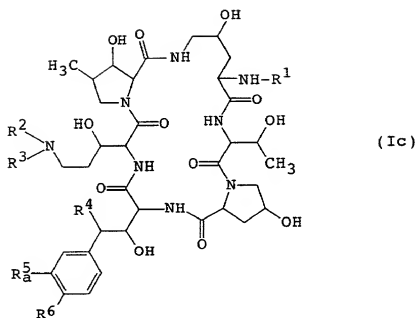
wherein R^1 , R^4 , R^5 and R^6 are defined in claim 1,

R_a^2 is hydrogen, lower alkyl which may have one or more suitable substituent(s), acyl group, heterocyclic group which may have one or more suitable substituent(s), lower alkylidenyl which may have one or more suitable substituent(s) or cyano and

R_a^3 is lower alkyl which may have one or more suitable substituent(s), acyl group, heterocyclic group which may have one or more suitable substituent(s), lower alkylidenyl which may have one or more suitable substituent(s) or cyano,

or a salt thereof, or

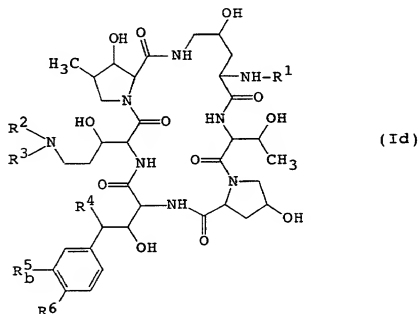
iii) subjecting a compound (Ic) of the formula:



wherein R^1 , R^2 , R^3 , R^4 and R^6 are defined in claim 1,
and

R^5_a is hydroxysulfonyloxy,

or a its reactive derivative at the sulfonic acid group,
or a salt thereof, to hydrolysis reaction of the
sulfonic acid group, to give a compound (Id) of the
formula:



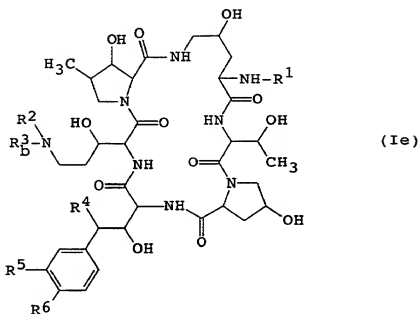
wherein R^1 , R^2 , R^3 , R^4 and R^6 are defined in claim 1,
and

R^5 is hydroxy,
or a salt thereof, or

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iv) subjecting a compound (Ie) of the formula:

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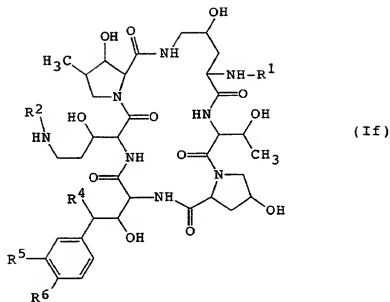
wherein R^1 , R^2 , R^4 , R^5 and R^6 are defined in claim 1,
and

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R^3 is amino protective group,
or a salt thereof, to elimination reaction of amino
protective group, to give a compound (If) of the
formula:

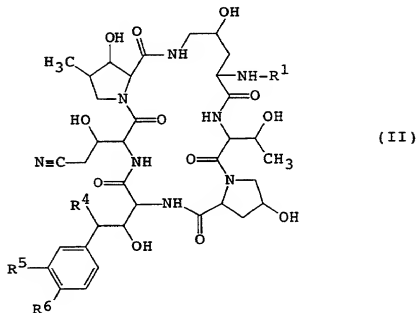
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wherein R¹, R², R⁴, R⁵ and R⁶ are defined in claim 1,
or a salt thereof.

v) reducing a compound (II) of the formula:

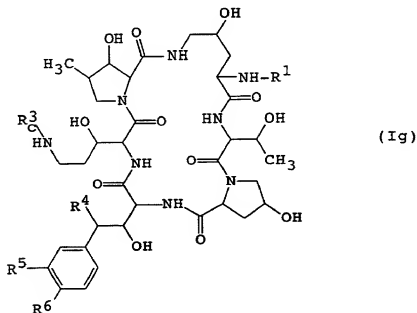


wherein R¹, R⁴, R⁵ and R⁶ are defined in claim 1,

or its reactive derivative or a salt thereof, and then reacting with a compound (IV) of the formula.

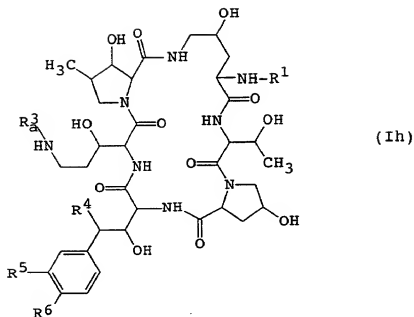


wherein R_C^3 is acyl group,
or its reactive derivative or a salt thereof,
to give a compound (Ig) of the formula:



wherein R^1 , R^4 , R^5 and R^6 are defined in claim 1, and
 R_C^3 is acyl group,
or a salt thereof, or

vi) reacting a compound (Ih) of the formula:



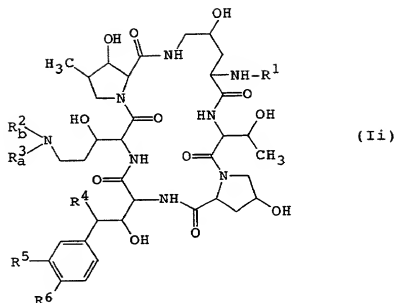
15 wherein R¹, R⁴, R⁵ and R⁶ are defined in claim 1, and
 R³_a is lower alkyl which may have one or more
 suitable substituent(s), acyl group,
 heterocyclic group which may have one or
 more suitable substituent(s), higher
 20 alkyl which may have one or more suitable
 substituent(s) or cyano,
 or its reactive derivative or a salt thereof, with a
 compound (V) of the formula:



wherein R²_B is acyl group,
 or its reactive derivative or a salt thereof,
 to give a compound (Ii) of the formula:

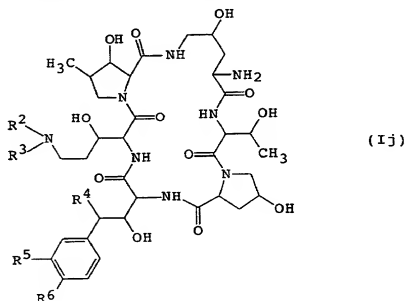
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wherein R^1 , R^4 , R^5 and R^6 are defined in claim 1,
 R^3_a is lower alkyl which may have one or more
 suitable substituent(s), acyl group,
 heterocyclic group which may have one or
 more suitable substituent(s), higher
 alkyl which may have one or more suitable
 substituent(s) or cyano, and
 R^2_b is acyl group, or a salt thereof, or

vii) reacting a compound (Ij) of the formula:



wherein R^2 , R^3 , R^4 , R^5 and R^6 are defined in claim 1, or its reactive derivative at the amino group, or a salt thereof, with a compound (III) of the formula:

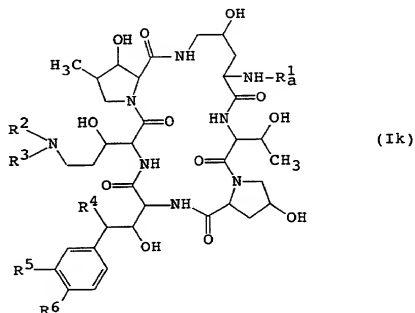


wherein R_a^1 is acyl group, or its reactive derivative at the carboxy group, or a salt thereof, to give a compound (Ik) of the formula:

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25 wherein R^2 , R^3 , R^4 , R^5 and R^6 are defined in claim 1, and

R_a^1 is acyl group.

9. A pharmaceutical composition which comprises, as an
30 active ingredient, a compound of Claim 1 or a pharmaceutically acceptable salt thereof in admixture with pharmaceutically acceptable carrier or excipients.

10. Use of a compound of Claim 1 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament.
- 5 11. A compound of Claim 1 or a pharmaceutically acceptable salt thereof for use as a medicament.
12. A method for the prophylactic and/or therapeutic treatment of infectious diseases caused by pathogenic microorganisms, which comprises administering a compound of claim 1 or a pharmaceutically acceptable salt thereof to a human being or an animal.
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Declaration, Power Of Attorney and Petition

Page 1 of 3

WE (I) the undersigned inventor(s), hereby declare(s) that:

My residence, post office address and citizenship are as stated below next to my name,

We (I) believe that we are (I am) the original, first, and joint (sole) inventor(s) of the subject matter which is claimed and for which a patent is sought on the invention entitled

CYCLIC HEXAPEPTIDES HAVING ANTIBIOTIC ACTIVITY

the specification of which

☐ is attached hereto.

☐ was filed on _____ as
Application Serial No. _____
and amended on _____.

☐ was filed as PCT international application

Number PCT/JP00/02710
on April 25, 2000,
and was amended under PCT Article 19
on _____ (if applicable).

We (I) hereby state that we (I) have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

We (I) acknowledge the duty to disclose information known to be material to the patentability of this application as defined in Section 1.56 of Title 37 Code of Federal Regulations.

We (I) hereby claim foreign priority benefits under 35 U.S.C. § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed. Prior Foreign Application(s)

Application No.	Country	Day/Month/Year	Priority Claimed
<u>PP9997</u>	<u>Australia</u>	<u>27/04/99</u>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
_____	_____	_____	<input type="checkbox"/> Yes <input type="checkbox"/> No
_____	_____	_____	<input type="checkbox"/> Yes <input type="checkbox"/> No
_____	_____	_____	<input type="checkbox"/> Yes <input type="checkbox"/> No

We (I) hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below.

(Application Number)	(Filing Date)
(Application Number)	(Filing Date)

We (I) hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

Application Serial No.	Filing Date	Status (pending, patented, abandoned)
PCT/JP00/02710	April 25, 2000	

And we (I) hereby appoint: Norman F. Oblon, Reg. No. 24,618; Marvin J. Spivak, Reg. No. 24,913; C. Irvin McClelland, Reg. No. 21,124; Gregory J. Maier, Reg. No. 25,599; Arthur I. Neustadt, Reg. No. 24,854; Richard D. Kelly, Reg. No. 27,757; James D. Hamilton, Reg. No. 28,421; Eckhard H. Kuesters, Reg. No. 28,870; Robert T. Pous, Reg. No. 29,093; Charles L. Gholz, Reg. No. 26,395; William E. Beaumont, Reg. No. 30,996; Jean-Paul Lavalleye, Reg. No. 31,451; Stephen G. Baxter, Reg. No. 32,884; Richard L. Treanor, Reg. No. 36,379; Steven P. Weihrouch, Reg. No. 32,829; John T. Goolkasian, Reg. No. 26,142; Richard L. Chinn, Reg. No. 34,305; Steven E. Lipman, Reg. No. 30,011; Carl E. Schlier, Reg. No. 34,426; James J. Kulbaski, Reg. No. 34,648; Richard A. Neifeld, Reg. No. 35,299; J. Derek Mason, Reg. No. 35,270; Surinder Sachar, Reg. No. 34,423; Jeffrey B. McIntyre, Reg. No. 36,867; William T. Enos, Reg. No. 33,128; Michael E. McCabe, Jr., Reg. No. 37,182; Bradley D. Lytle, Reg. No. 40,073; and Michael R. Casey, Reg. No. 40,294; our (my) attorneys, with full powers of substitution and revocation, to prosecute this application and to transact all business in the Patent Office connected therewith; and we (I) hereby request that all correspondence regarding this application be sent to the firm of OBLON, SPIVAK, MCCLELLAND, MAIER & NEUSTADT, P.C., whose Post Office Address is: Fourth Floor, 1755 Jefferson Davis Highway, Arlington, Virginia 22202.

We (I) declare that all statements made herein of our (my) own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

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